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THE SURGICAL MANAGEMENT OF CHOLECYSTITIS EMPHYSEMATOSA*

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CHOLECYSTITIS emphysematosa, sometimes called acute gaseous cholecystitis, pyopneumocholecystitis or gas phlegmon of the gallbladder, is an inflammation of the gallbladder with grossly discernible gas formation. It is a rare condition, although possibly not quite as rare as the small number of reported cases would indicate. This form of acute gangrenous cholecystitis is characterized by the presence of gas in the gallbladder lumen, biliary ducts, wall and pericholecystic tissue.

The phenomenon of cholecystitis emphysematosa was first reported as an operative finding by Lobingier[1] in 1908. The first recorded preoperative roentgenographic diagnosis was made by von Friederich[2] in 1929. Since that time a few operative reports and reviews[3-5] have appeared in the literature. Since last reporting on this subject,[6] two additional cases have come to the author's attention at the Buffalo General Hospital. In addition 33 previously reported cases have been studied. Contrary to the findings in these reported cases, the author's experience would suggest that this complication of acute cholecystitis appears more commonly in diabetics; this suggests that arteriosclerosis and the tendency to thrombosis found in diabetics might play an etiologic role. It is again suggested that it will be more frequently encountered with our ageing diabetic population and with the increasing widespread use of the roentgenogram in evaluating the acute abdomen. (See Table I.)

The disease has been reported in patients between the ages of 27 and 73, but it occurs most frequently between the fifth and seventh decades, and thus is a problem of a somewhat older age group than the usual type of acute cholecystitis. More than 50% of the cases reviewed were reported to have a previous history of either acute or chronic attacks of cholecystitis. The incidence of associated cholelithiasis, as suspected, is high. In the author's experience choledocholithiasis has been noted in three out of four cases.

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ETIOLOGY AND PATHOGENESIS

The contributing factors leading to the development of acute cholecystitis and subsequent gas infection are protean. The prime factor is a permanent or temporary obstruction of the cystic duct which is usually due to a calculus either within the cystic duct or impacted in Hartmann's pouch. However, other factors such as angulation of kinks of the duct, anomalous blood vessels, adhesions, enlarged lymph nodes, tumours, inflammation and vascular occlusion may be responsible. The inflammation may be either chemical or infectious. The latter is usually a secondary phenomenon with bacteria invading the already edematous gallbladder by the blood stream, lymphatics or biliary tree.

Bacteria may be cultured from the walls of 45% of gallbladders removed for acute cholecystitis and from the bile of 29% of such cases.[7] Many different organisms have been isolated. The most common have been *Escherichia coli*, *Bacterium aerogenes* (*Aerobacter aerogenes*), nonhemolytic streptococcus, Clostridium and Klebsiella. In all previously reported cases of cholecystitis emphysematosa, where bacteriologic studies were carried out on specimens received at the time of operation or at necropsy, anaerobic, gas-forming microorganisms, usually of the *Clostridium welchii* type, were cultured. Branch[8] isolated *Clostridium welchii* from 8% of the walls, 7% of the stones, and 5% of the bile fluids of surgically removed gallbladders. Gordon-Taylor and Whitby[9] found *Clostridium welchii* in 18% of gallbladders routinely studied. Andrews and Henry[10] concluded that *Clostridium welchii* was commonly present in the bile of both normal and diseased gallbladders. Thorsness[11] has shown that many of these strains are attenuated, non-sporulating and consequently of a low virulence. This lends support to the existence, as some have claimed, of bacteriostatic properties within the bile.

When the environment is suitable and the tissue oxygen tension is reduced by one means or another, gas slowly accumulates within the gallbladder and surrounding structures. The usual history of a period of 24 to 48 hours would suggest that the gas-producing organisms are actually secondary invaders,[12] but once established they appear able

TABLE I.—Previously Reported and Author's Cases of Cholecystitis Emphysematosa

Author and date	*Sex and age*	*History of previous attacks*	*Diabetes*	*X-rays*	*Initial treatment*	*Chole-lithiasis*	*Chole-docho-lithiasis*	*Procedure*	*Follow-up*
Lobingier, 1908[1]	M 55	Yes	No	Not done	Operative	Single stone	—	Chole-cystectomy	Recovery
Tanner, 1921[17]	M 44	—	No	Not done	Operative	None	None	Chole-cystectomy	Recovery
Kirchmayr, 1925[18]	M 64	No	No	Not done	Conservative	Many	—	Chole-cystectomy	Recovery
Hegner, 1931[19]	M 62	Yes	No	Gas in the gallbladder	Conserva-tive	Single stone	—	Chole-cystectomy	Died, pulm. embolus 4th postop. day
Simon, 1932[20]	M 32	No	No	Gas in the gallbladder	Conserva-tive	Many	—	Chole-cystectomy	Recovery
Wybauw, 1936[21]	F 53	Yes	No	Cholelithiasis outlined by gas	Conserva-tive	Many	—	Chole-cystectomy	Recovery
Schmidt, 1938[22]	M 38	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	None	Recovery
del Campo and Ote 1940[35]	M 74	No	No	Gas in the G.B., C.D. and biliary passages	Conserva-tive	Many	Yes	Chole-cystectomy	Died 4th postop. day
McCorkle and Fong, 1942[12]	M 49	Yes	No	Gas in the gallbladder	Operative	Single stone	—	Chole-cystectomy	Died 48 hrs. postop.
	M 59	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	None	Recovery
	M 49	No	Yes	Gas in the gallbladder	Conserva-tive	—	—	None	Recovery
Stevenson, 1944[23]	M 64	No	Yes	Gas in the gallbladder	Conserva-tive	Many	—	Chole-cystectomy	Recovery
	M 63	No	No	Gas in the gallbladder	Conserva-tive	Single stone	—	Chole-cystectomy	Recovery
	M 52	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	None	Recovery
Hutchinson, 1946[24]	M 56	No	No	Not done	Conserva-tive	Yes	—	Chole-cystectomy	Recovery
Heifetz and Senturia, 1948[25]	M 52	Yes	No	Gas in the gallbladder	Conserva-tive	Many	—	Cholecyst-ostomy	Recovery
	F 57	Yes	No	Gas in G.B. and stones	Conserva-tive	Many	—	Chole-cystectomy	Recovery
Friedman, Aurelius and Rigler, 1949[26]	F 53	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	Chole-cystectomy	Recovery
	M 68	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	None	Recovery
	M 66	No	Yes	Gas in G.B. and ducts	Conserva-tive	—	—	None	Recovery
	F 65	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	None	Recovery
Jemerin, 1949[7]	F 68	No	No	Gas in the gallbladder	Conserva-tive	Many	None	Cholecyst-ectomy	Died, C.V.A. 24th postop. day
Gowdey and Copeland, 1950[27]	M 57	Yes	No	Gas in the gallbladder	Conserva-tive	—	—	Cholecyst-ectomy	Recovery
Elsey and Hudson, 1950[33]	M 75	No	—	Gas in the region of gallbladder	Operative	None	None	Chole-cystostomy	Recovery
Retterbush *et al.*, 1951[28]	M 65	No	No	Gas in the gallbladder	Operative	Many	—	Chole-cystectomy	Recovery
Qvist, 1951[29]	M 61	No	No	Gas in the gallbladder	Operative	None	Yes	Chole-cystostomy	Recovery

TABLE I.—*Continued*

Author and date	*Sex and age*	*History of previous attacks*	*Diabetes*	*X-rays*	*Initial treatment*	*Cholelithiasis*	*Choledocholithiasis*	*Procedure*	*Follow-up*
Ryan, Harrigan and Penny, 1953[30]	M 70	No	No	Gas in the region of G.B. and in wall	Operative	None	Yes	Cholecystectomy	Recovery
Strömme, 1955[5]	M 27	No	No	Gas in G.B. and ducts	Conservative	—	None	None	Recovery
Wilson, 1957[3]	M 43	Yes	No	Gas in the gallbladder	Conservative	—	—	None	Recovery
McLachlin, Chapman and Carroll, 1958[34]	M 66	—	—	Gas in the gallbladder	Conservative	None	None	Cholecystectomy	Recovery
von V. Bobrengier, 1958	F 47	Yes	No	Gas in the gallbladder	Conservative	Yes	None	Cholecystostomy	Recovery
Farpair, 1959	M 69	Yes	No	Gas in biliary ducts	Conservative	—	—	Cholecystectomy	Recovery
McGregor, Brown and Milch[6, 32]	M 60	Yes	Yes	Gas shadow in region of gallbladder	Conservative	None	None	None	Died 5 weeks after onset of acute attack
McGregor[6]	F 76	Yes	Yes	Gas in G.B.+ biliary ducts	Operative	Yes	Yes	Cholecystostomy, 5 wks. later cholecystectomy +C.D. expl.	Alive and well 2 years postop.
	M 73	Yes	Yes	Gas in G.B. wall	Operative	Yes	Yes	Cholecystectomy	Alive and well 8 mos. postop.
	M 64	Yes	No	Gas in region of G.B.	Operative	Yes	Yes	Cholecystectomy	Alive and well 6 mos. postop.

to travel along interstitial tissue planes and are often found well beyond the gangrenous area.

The method by which these organisms gain access to the gallbladder has been in some dispute, but Mason and Hart[13] have been able to culture *Clostridium welchii* constantly from normal human livers, a feat duplicated by Markowitz[14] in the dog. In all probability, these organisms gain access via the portal circulation. Those that survive phagocytosis pass into the bile canaliculae and thence via the bile to the gallbladder, or else they enter the liver lymphatics and are able to pass directly to the gallbladder by way of the rich communicating lymphatic network between these organs.

If the environment changes and gas-forming organisms begin to sporulate, gaseous infiltration of the wall occurs. This appears on roentgenograms as a thin, radiolucent layer immediately peripheral to the lumen of the gallbladder. Later, gas may be detected in the region of the gallbladder as a radiolucent area similar to that seen in the bowel wall in cases of pneumatosis cystoides intestinalis.[15] At this time there is probably a marked pericholecystitis. If the infection subsides, the gas is generally absorbed or possibly discharged through the cystic duct.

As the disease progresses, the wall and surrounding tissue become crepitant. The gallbladder lumen fills with infected fluid and gas which may produce a fluid level on roentgen studies. Finally the trapped gas within the wall disseminates through the tissues and appears on roentgen studies as numerous, short, radiolucent strata. Some observers have suggested that these strata represent air-filled Rokitansky-Aschoff sinuses. However, experimental studies have shown that more likely they represent perimuscular air, appearing first near the cystic duct and spreading to the fundus.

DIAGNOSIS

The clinical features are essentially those of an acute cholecystitis of 24 to 48 hours' duration, and the clinician is confronted with the differential diagnosis of an acute abdomen. In recent years the radiologist has contributed greatly to the evaluation of the acute abdomen, has made it possible to confirm many clinically suspected diagnoses, and has produced some which were heretofore unsuspected. It is important to differentiate this lesion from a fistulous communication with the gastrointestinal tract. When such a communication is the cause of air in the biliary tree, the gallbladder is usually of normal size or smaller, and the biliary duct system as well as the gallbladder casts a gaseous shadow on the roentgenogram. This is in contrast to the enlarged gallbladder shadow, surrounded by a denser ring representing the gas within the wall, that characterizes gaseous cholecystitis. A duodenal cap distended with gas may resemble a gas-filled gallbladder. In questionable and obscure cases barium

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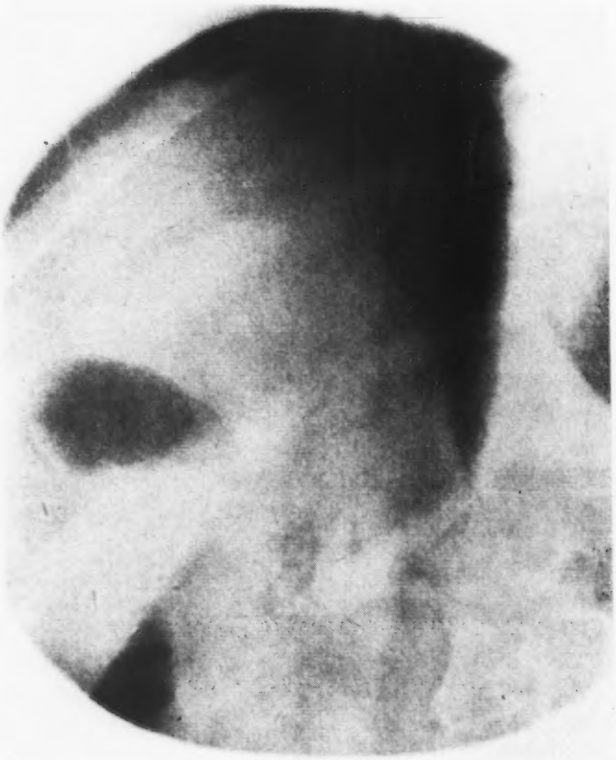

Fig. 1.—Flat plate of the abdomen revealing gas in the vicinity of the gallbladder, suggestive of gaseous cholecystitis.

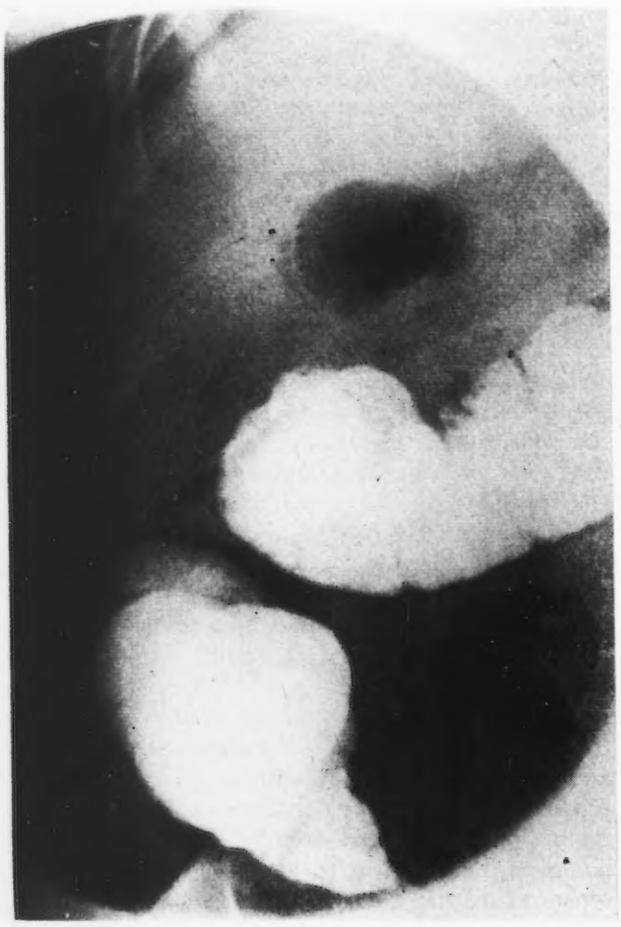

Fig. 2.—Barium enema outlining the hepatic flexure of the colon of the same patient as in Fig. 1. This study reveals no fistulous connection between the colon and the gallbladder.

enema examination and an upper gastrointestinal series will be of value in ruling out cholecystoenteric or choledochoenteric fistulae, or incompetent valve mechanisms at the lower end of the biliary tree. Lipomas of the gallbladder wall have occasionally been cited as casting a similar ring shadow on roentgenograms, but this is a rarely reported occurrence and may be differentiated by the absence of gas within the lumen and the lack of day-to-day change.

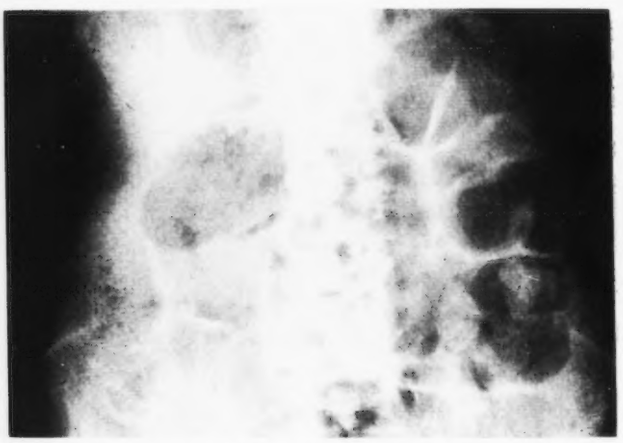

Fig. 3.—Flat plate of an acute abdomen with visualization of gas in the gallbladder, associated with an intestinal ileus. The gas appears stratified about the periphery, suggesting distension of the Rokitansky-Aschoff sinuses.

TREATMENT

In the past some authors[4, 12] have suggested that these patients are best managed by conservative means. It does not seem that fundamental surgical principles are being satisfied by permitting a diseased, infected, stone-containing gallbladder, which would be removed in any other circumstance, to remain *in situ* because the infecting organism is *Clostridium welchii*. This is particularly so because the inflammation is frequently associated with gangrene going on to destruction of the gallbladder wall, and pericholecystitis or abscess formation. Moreover, if chemotherapy can stop the spread of infection without the need for operation, it should be equally effective in preventing extension within the abdomen during the postoperative period. The mortality and morbidity have been shown to rise appreciably, the longer operation is deferred. In the group of patients in which prolonged conservative therapy was undertaken, the mortality and morbidity rates were noted to be higher than in the group subjected to early operation. When the diagnosis is made and operation is decided upon, treatment should be directed as rapidly as possible to preparing the patient for surgery by correcting the electrolyte deficits, if any, and stabilizing the diabetes if this is a factor. Attention should also be directed toward the gas infection, which is frequently characterized by gross blood destruction, even to the point of clinical jaundice. Preoperative transfusion with fresh whole blood is desirable, if indicated by preoperative hemoglobin and hemato-

crit levels. Penicillin has been the most successful single factor in controlling gas infection, and the use of 40,000,000 to 60,000,000 units per day plus a daily dose of 90 to 100 ml. of polyvalent anti-gas-gangrene serum by intravenous and intramuscular routes should be administered, although the latter measure rests on less solid foundations than the use of antiserum in tetanus.

It is the author's belief that initially these are cases of gas-filled abscess rather than gas cellulitis (or myositis), and that the gas-forming organisms are secondary invaders of the gallbladder wall. Fear of surgical manipulation, which is expressed by some authors, does not seem justified. This procedure does not produce a sustained bacteremia and subsequent septicemia. It has been shown that such bacteremias are quickly suppressed and that an anaerobic state is required for spore germination and growth. To produce the classical foaming liver experimentally, the animal must be killed shortly after injection and incubated for some eight hours prior to necropsy.[16] Thus cholecystectomy is always the operation of choice, particularly in the early stages of the disease, for it removes the medium of infection and the tissue most susceptible to invasion by anaerobic organisms. Frequently subhepatic and subdiaphragmatic collections of fluid are present, and postoperative drainage of these spaces is felt to be mandatory. However, factors presenting in the individual case must be considered by the surgeon, and his judgment must be based accordingly.

Conclusions

Cholecystitis emphysematosa is a relatively rare manifestation of acute cholecystitis.

Diabetes mellitus appears to predispose the patient to this complication of acute cholecystitis.

The incidence of concomitant common duct stones appears high in our limited experience.

The growth of the gas-forming organisms is secondary to the initial development of acute cholecystitis.

The differential diagnosis between cholecystitis emphysematosa and cholecystoenteric fistula can be made on the basis of a plain roentgenogram and confirmed, if required, by an upper gastrointestinal barium enema examination.

Early cholecystectomy is the treatment of choice, but the surgeon must be governed by factors presenting in the individual case, and a lesser drainage procedure may be indicated in some cases.

The use of heavy antibiotic therapy and anti-gas-gangrene serum improves the prognosis remarkably.

Summary

The literature concerning cholecystitis emphysematosa is briefly reviewed. Four cases are reported; three of the patients were diabetics over 60 years of age. It is felt that, in the future, the ageing diabetic patients will contribute significantly to the incidence of this disease. Cholecystitis emphysematosa is characterized by the development of a gas-containing abscess in the gallbladder. The majority of cases occur in the age group in which acute cholecystitis is most frequently encountered. Although some cases have been reported to resolve spontaneously[12] with medical therapy, it is the author's belief that the overall mortality and morbidity can be reduced by early operation, the operation of choice being cholecystectomy performed while the patient is receiving massive antibiotic and anti-gas-gangrene therapy.

Reference

1 LOBINGIER, A. S.: *Ann. Surg.*, **48:** 72, 1908.
2. VON FRIEDERICH, L.: Cited in: *Radiology*, **50:** 536, 1948.
3. WILSON, W. A.: *Brit. J. Surg.*, **45:** 333, 1958.
4. MOONEY, B. R. AND MATZINGER, K. E.: *Canad. M. A. J.*, **66:** 66, 1952.
5. STRÖMME, A.: *Acta radiol.*, **44:** 39, 1955.
6. McGREGOR, J. K.: *A.M.A. Arch. Surg.*, **81:** 558, 1960.
7. JEMERIN, E. E.: *Surgery*, **25:** 237, 1949.
8. BRANCH, C. E.: *New England J. Med.*, **201:** 308, 1929.
9. GORDON-TAYLOR, G. AND WHITBY, L. E. H.: *Brit. J. Surg.*, **18:** 78, 1930.
10. ANDREWS, E. AND HENRY, L. D.: *Arch. Int. Med.*, **56:** 1171, 1935.
11. THORSNESS, E. T.: *Surg. Gynec. & Obst.*, **59:** 752, 1934.
12. McCORKLE, H. AND FONG, E. E.: *Surgery*, **81:** 851, 1942.
13. MASON, E. C. AND HART, M. S.: *J. Lab. & Clin. Med.*, **25:** 835, 1940.
14. MARKOWITZ, J.: *Surg. Gynec. & Obst.*, **95:** 644, 1952.
15. McGREGOR, J. K. AND McKINNON, D. A., JR.: *Gastroenterology*, **35:** 206, 1958.
16. DUBOS, R. J., Editor: Bacterial and mycotic infections of man, 2nd ed., J. B. Lippincott Company, Philadelphia, 1952, p. 395.
17. TANNER, E. K.: *Surg. Gynec & Obst.*, **32:** 468, 1921.
18. KIRCHMAYR, L.: Cited in: *Gastroenterology*, **10:** 626, 1948.
19. HEGNER, C. F.: *Arch. Surg.*, **22:** 993, 1931.
20. SIMON, J.: *Presse méd.*, **40:** 1938, 1932.
21. WYBAUW, L.: Cited in: *Brit. J. Surg.*, **45:** 333, 1958.
22. SCHMIDT, E. A.: *Radiology*, **31:** 423, 1938.
23. STEVENSON, C. A.: *Am. J. Roentgenol.*, **51:** 53, 1944.
24. HUTCHINSON, W. R. S.: *Brit. M. J.*, **1:** 915, 1946.
25. HEIFETZ, C. J. AND SENTURIA, H. R.: *Surg. Gynec & Obst.*, **86:** 424, 1948.
26. FRIEDMAN, J., AURELIUS, J. R. AND RIGLER, L. G.: *Am. J. Roentgenol.*, **62:** 814, 1949.
27. GOWDEY, J. F. AND COPELAND, N. N.: *New England J. Med.*, **242:** 647, 1950.
28. RETTERBUSH, W. C. *et al.*: *Ann. Surg.*, **134:** 268, 1951.
29. QVIST, C. F.: *Acta radiol.*, **35:** 200, 1951.
30. RYAN, E. A., HARRIGAN, E. AND PENNY, S. F.: *Canad. M. A. J.*, **69:** 606, 1953.
31. FARPOUR, A., LEIVY, F. E. AND ULIN, A. W.: *J. Albert Einstein M. Center Bull.*, **7:** 120, 1959.
32. BROWN, R. K. AND MILCH, E.: *Gastroenterology*, **10:** 626, 1948.
33. ELSEY, E. C. AND HUDSON, H. C.: *Am. J. Roentgenol.*, **63:** 228, 1950.
34. McLACHLIN, J., CHAPMAN, D. J. AND CARROLL, S. E.: *Med. Serv. J., Canada*, **14:** 757, 1958.
35. DEL CAMPO, J. C. AND OTERO, J. P.: Cited in: *Brit. J. Surg.*, **45:** 333, 1958.

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PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

Occasionally one meets with people who, after one or more attacks of appendicitis, are never well, but suffer from vague abdominal pains, dyspepsia, and even chronic invalidism. There is frequently a hypochondriacal and neurasthenic factor superadded. These patients are very hard to manage and frequently have gone the round of many practitioners, and been treated under many diagnoses with unsatisfying results. Much has been written upon this subject lately, and the influence of an erring appendix with its adhesions has probably been over-emphasized. Still, in many instances, the removal of the appendix has brought about a cure. Hence, in such cases, the possibility of the trouble being primarily in the appendix should be borne in mind, and if the condition resists the influence of a careful course of medicinal and dietetic treatment, then the removal of the appendix should be advised.—Robert D. Rudolf, *Canad. M. A. J.*, 1: 927, 1911.

A METHOD FOR THE ESTIMATION OF IN VITRO SURVIVAL OF HUMAN MARROW CELLS, UTILIZING RADIOAUTOGRAPHIC DETECTION OF H^3-THYMIDINE UPTAKE*

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"THERE IS some doubt whether the leukocytes in stored blood are still alive and functional."[5] The earlier reports on the viability of the white blood cells were based on the characteristics of cell motility[1-5] or morphology.[6, 7] In recent years, the radioactive isotopes have been used by many workers. Estimation of *in vitro* survival has been based on the ability of the cells to synthesize Fe^{55} and Fe^{59} [8, 9] and C^{14}-labelled aminoacids;[10] however, most of the literature is related to the synthesis of nucleic acids. This has been detected by the *in vitro* incorporation of P^{32},[11, 9] C^{14} formate[11-15] C^{14} thymidine[16, 18] and most recently, H^3 thymidine.[17, 20] A routine method based on the incorporation of H^3 thymidine into desoxyribonucleic acid (DNA) by human marrow cells and its radioautographic recording is described in this report.

TECHNICAL PROCEDURE

Human marrow obtained by aspiration from the iliac crest was mixed with an equal volume of heparinized Connaught experimental medium M 150 and refrigerated to 4° C. A 2-ml. sample was mixed after intervals of one hour to four days with 0.5 ml. M 150 containing between 40 and 60 μc. H^3 thymidine with a specific activity of 1.9C/mM. The labelled sample was placed in a culture tube and rotated slowly for one hour at room temperature. The erythrocytes were then sedimented with 6% dextran; the supernatant was centrifuged at 600 G. for three minutes. Smears made from the sediment were fixed in acetic-ethanol (1:3) and dried overnight. After Feulgen staining, the smears were dipped in 0.3% celloidin and dried. Integrated radioautographs (21) were obtained, utilizing Eastman's NTB3 melted emulsion and exposing at 4° C. for two months. The radioautographs were developed for 10 minutes in Kodak D19 diluted 1:1 with distilled water, rinsed and fixed in Kodak Acid Fixer with Hardener, this whole process taking place in a water bath at 4° C. They were then washed in running water for 30 minutes, dried in front of an electric fan and eventually covered with a thin coverslip and Permount (Fisher).

The preparations were examined and a minimum of 1000 cells was counted at 500 times magnification. The percentage of labelled cells was considered to represent the ability of cells in a given aspirate to synthesize DNA, and presumably to proliferate. By varying the conditions of collection and incubation, some of the factors which affect the H^3-thymidine uptake of marrow cells *in vitro* could be isolated.

RESULTS AND COMMENTS

H^3-Thymidine

Thymidine is a specific precurser of DNA. It becomes incorporated into the nucleic acid molecule during a short period which immediately precedes prophase.[22] Consequently the identification of labelled DNA indicates not only that the cell metabolizes organic material but that it is also preparing to divide. The isotope tritium (H^3) incorporated into thymidine emits beta particles of low energy (0.019 mev.) and permits high resolution radioautographs.[22]

General appearance of radioautographs

A typical field, such as that in Fig. 1, shows some strongly labelled nuclei dispersed amongst a majority of non-labelled cells. Most of the labelled nuclei belong to the larger cells in a normal preparation. Staining of the nuclei by the Feulgen method has proved essential, since this operation removes all labelled thymidine which has not been incorporated into DNA, as evidenced by the low background.

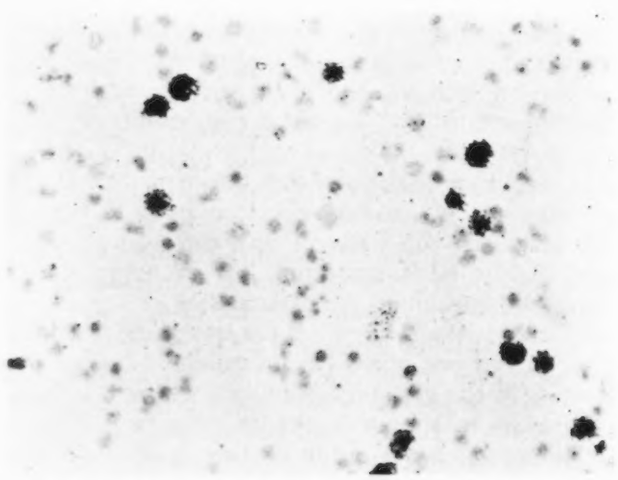

Fig. 1.—Integrated radioautograph from a Feulgen-stained smear of marrow cultured after three hours at 4° C. The majority of labelled nuclei are large. × 500.

The cells have not been specifically identified in the present studies. However, the shape and relative size of both labelled and non-labelled cells can be easily recognized (Fig. 1).

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Counts on marrow specimens from different individuals

The following counts were obtained on specimens taken from four patients and refrigerated for three hours at 4° C. before culturing (Table I).

TABLE I.

Patient	*Labelled cells*
A	14.8%
B	8.0%
C	7.2%
D	8.7%

In spite of the similarity of results, particularly in the last three, it is evident that quantitative comparisons between different individuals and even between specimens taken at different times from the same patient are *not valid* because of the unpredictable amount of peripheral blood dilution in different aspirates.

Counts on aliquots of a single marrow specimen

Marrow obtained by aspiration from one donor was divided into four aliquots (A, B, C, D) as shown in Table II. The following conclusions can be drawn from study of these results.

TABLE II.

Specimen and treatment	*Labelled cells* *M1*	*M2*	*M3*
A: refrigerated at 4°C. for 1 hr., cultured 1 hr.	15.0%	8.8%	10.1%
B: refrigerated at 4°C. for 1 hr., cultured 24 hrs.	19.0%	18.8%	21.9%
C: refrigerated at 4°C. for 3 hrs., cultured 1 hr.	13.5%	15.0%	15.9%
D: refrigerated at 4°C. for 24 hrs., cultured 1 hr.	15.0%	10.7%	13.0%

1. *Counts* made by three different experienced microscopists, using one or several preparations from the same specimens, have revealed only minor variations (M1, M2, M3, Table II).

2. *Duration of culture period.*—Comparisons between specimens A and B in Table II have revealed that most of thymidine uptake takes place during the first hour of incubation, a fact already known to investigators making use of this label *in vivo*.[22]

3. *Period of refrigeration.*—For periods up to 24 hours at 4° C., the counts showed little variation (Table II). Radioautographs of specimen D (Table II) have revealed, however, a *considerable decrease in the intensity of the label* as compared with that of A and B, indicating that if a similar number of cells were capable of DNA synthesis, the rate of synthesis of the individual cells had been affected.

After 48 hours of refrigeration, the radioautographs of cultured specimens revealed practically no large labelled cells; there were a few small cells labelled, presumably normoblasts and lymphocytes. After three and four days there were practically no labelled cells. These results confirm the conclusions reached by Mannick *et al.*[14] on the storage of marrow at 4° C.

Centrifugation.—In order to appreciate the effect of centrifugation, one specimen was divided into four tubes, two of which were centrifuged at 600 G. for 15 minutes and the other two were cultured without centrifugation. The radioautographs yielded labelled cell counts of 7.2, 7.2, 7.9 and 7.8%, pointing to no adverse effect.

Heparin.—The heparin preparation used in this work has been Connaught Liquid Heparin, 1000 units per ml. This preparation contains 0.5% phenol; although heparin has been reported to have no effect on DNA synthesis[15] in concentrations up to 1.0 mg. per ml., phenol in concentrations of 0.023% (0.23 mg. per ml.) depressed DNA synthesis.[15] In order to study the effect of heparin and phenol concentrations, the following experiment was carried out. Marrow, 15 ml., was aspirated from the posterior iliac crest of a hematologically normal individual, into a siliconized syringe. After gentle mixing, 5 ml. of this aspirate was put through a needle with a screen in the hub, into two separate siliconized tubes at 4° C. Tube 1 contained 5 ml. of culture medium M-150 with a heparin concentration of 20 units per ml., i.e. a final concentration of 10 units per ml. The final phenol concentration in this tube was 0.005 g. % (0.05 mg. per ml.). Tube 2 contained 5 ml. of culture medium M-150 with a heparin concentration of 200 units per ml., i.e. a final concentration of 100 units per ml. The final phenol concentration in this tube was 0.05 g. % (0.5 mg. per ml.).

The radioautographs produced after three hours of refrigeration and one hour of culture yielded an average of 8.7% labelled cells for a total count of 4000 from tube 1 and 7.7% from tube 2. Consequently a concentration of 100 units of heparin or of 0.5 mg. of phenol per ml. of marrow M-150 mixture (1:1) could not be shown to have an adverse effect on DNA synthesis.

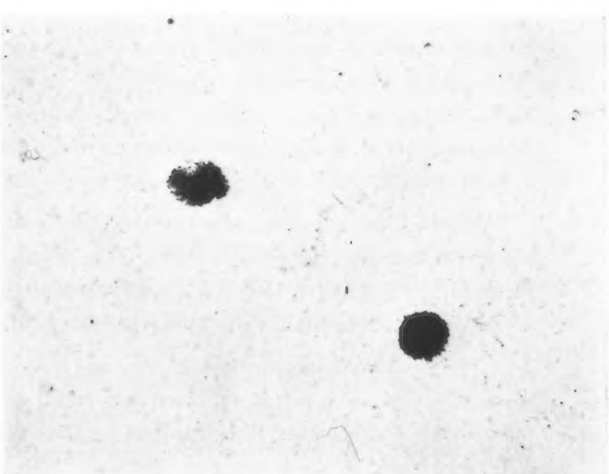

Fig. 2.—Radioautograph of two labelled myeloma cells, × 300.

Neoplastic marrow cells.—One specimen was collected from a patient suffering from multiple myeloma. The large multiform neoplastic cells were easily recognized in the smears. They produced strong records of H^3-thymidine uptake after three hours at 4° C. (Fig. 2). After 24 hours of refrigeration, no tracer uptake could be detected. This seems to indicate a shorter *in vitro* life span as compared to normal marrow cells.

CONCLUSIONS

The procedure described above appears to offer a reliable criterion for the appreciation of conditions which can affect the viability of marrow cells *in vitro*. It can be used for evaluation of the optimal conditions for collection, preservation and readministration of human bone marrow.

SUMMARY

A technique for obtaining radioautographs of *in vitro* uptake of H^3 thymidine by human marrow cells is described. On the basis of comparative percentage of labelled cells in smears, it has been established that marrow cells survive up to 48 hours at 4° C. in Morgan's M-150 culture medium. Myeloma cells were found to be more fragile than normal marrow cells. Centrifugation at 600 G. for 15 minutes, heparin concentrations of up to 100 units per ml., and 0.5 mg. of phenol per ml. of mixture, did not seem to affect viability.

The authors wish to express their gratitude to Dr. E. P. Cronkite and his associates of the Brookhaven National Laboratory for advice, to Eastman Kodak Co. (Rochester, N.Y.) for experimental nuclear emulsions, and to the Ontario Cancer Treatment and Research Foundation for a grant in aid. M 150, a modified TC199 with pH of 7.2, was kindly supplied by Dr. J. F. Morgan, Chief of the Biochemistry Division, Laboratory of Hygiene, Ottawa.

REFERENCES

1. SABIN, F. R. *et al.*: *Bull. Johns Hopkins Hosp.*, **37**: 14, 1925.
2. LEWIS, W. H.: *Ibid.*, **49**: 29, 1931.
3. CLARK, E. R., CLARK, E. L. AND REX, R. O.: *Am. J. Anat.*, **59**: 123, 1936.
4. BLOOM, W.: *In*: Handbook of hematology, Vol. I, edited by H. Downey, Paul B. Hoeber, Inc., New York, 1938, p. 375.
5. MACFARLANE, E. W. E.: *Proc. Soc. Exper. Biol. & Med.*, **56**: 32, 1944.
6. OSGOOD, E. E. AND BROWNLEE, I. E.: *J. A. M. A.*, **108**: 1793, 1937.
7. LAJTHA, L. G.: *J. Clin. Path.*, **5**: 67, 1952.
8. ELLIS, G. H., BRANDT, C. S. AND THACKER, E. J.: *Science*, **119**: 94, 1954.
9. SACCHETTI, C. *et al.*: *Minerva nucleare*, **3**: 213, 1959.
10. LAJTHA, L. G., OLIVER, R. AND ELLIS, F. H.: *Brit. J. Cancer*, **8**: 367, 1954.
11. LAJTHA, L. G.: *Nature*, **174**: 1013, 1954.
12. TOTTER, J. R. AND BEST, A. N.: *Arch. Biochem.*, **54**: 318, 1955.
13. THOMAS, E. D. AND LOCHTE, H. L., JR.: *Blood*, **12**: 1086, 1957.
14. MANNICK, J. A. *et al.*: *Ibid.*, **15**: 517, 1960.
15. LOCHTE, H. L., JR., FERREBEE, J. W. AND THOMAS, E. D.: *J. Lab. & Clin. Med.*, **55**: 435, 1960.
16. FRIEDKIN, M. AND WOOD, H. IV: *J. Biol. Chem.*, **220**: 639, 1956.
17. LAJTHA, L. G. AND OLIVER, R.: *Lab. Invest.*, **8**: 214, 1959.
18. PILERI, A., MARAINI, G. AND GAVOSTO, F.: *Boll. Soc. ital. biol. sper.*, **35**: 631, 1959.
19. GAVOSTO, F., PILERI, A. AND MARAINI, G.: *Ibid.*, **35**: 627, 1959.
20. OSGOOD, E. E.: *Ann. New York Acad. Sc.*, **77**: 777, 1959.
21. BÉLANGER, L. F. AND LEBLOND, C. P.: *Endocrinology*, **39**: 8, 1946.
22. CRONKITE, E. P. *et al.*: *Ann. New York Acad. Sc.*, **77**: 803, 1959.

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FURTHER STUDIES ON MERALGIA PARESTHETICA*

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THE PURPOSE of this paper is to present an interim report concerning the anatomical abnormalities that may be found in the disease called meralgia paresthetica. A clear understanding of the anatomical variants of the lateral cutaneous nerve of the thigh cannot be obtained from the study of most textbooks of anatomy or surgery. Since the publication of our first report on this condition in this Journal in May of 1959,[1] we have seen a relatively large number of cases, and are in the process of dissecting one hundred legs to determine the variations in the anatomy of this nerve. Meralgia paresthetica was first described by Bernhardt[2] in 1895 and the name was applied by Roth[3] in the same year. The term is derived from the Greek words "meros"—thigh, and "algos"—pain; thus, from its literal translation, the disease is characterized by pain in the thigh. A classical description of the disease includes pain in the distribution of the lateral femoral cutaneous nerve (Fig. 1); this pain may be in the form of formication, coldness, burning, or lightning pains, which may progress to hypoesthesia or frank anesthesia. Classically, these symptoms are produced in the erect or the supine position and are relieved by flexing the thigh.

On continued observation of this syndrome, we have noted that many patients present with severe and bizarre types of pain over the lateral aspect of the thigh which may be so severe that the victims are incapacitated. The patient may walk with a limp that closely mimics that of actual hip joint disease. The severity of the pain experienced by some of these patients is greatly in excess of that previously reported in this disease entity. The patient with the most severe symptoms that we have seen was a physician; and both legs were involved. When the symptoms were particularly disturbing, the patient required 400 mg. of barbiturate and 100 mg. of meperidine (Demerol) before he could get two or three hours' sleep at night.

ANATOMY

The lateral cutaneous nerve of the thigh is a sensory branch derived from the posterior roots of L2 and L3. Emerging from the lateral border of the psoas muscle, the nerve crosses the iliacus muscle deep to the iliac fascia to reach the anterior superior iliac spine; just before reaching this point, the nerve emerges to lie superficial to the iliac fascia (Fig. 2).

The nerve passes into the thigh just medial to the anterior superior iliac spine but posterior to the lateral end of the inguinal ligament and anterior to the iliacus muscle. Normally the nerve can be found approximately 1.5 to 2 cm. distal to the inguinal ligament in a groove between the sartorius iliacus muscles. The nerve measures 2 to 3 mm. in diameter and is larger than the size or the importance of its sensory distribution would indicate; it is always surrounded by a liberal amount of fat and is accompanied by a small artery. Approximately 10 cm. distal to the inguinal ligament, the nerve pierces the fascia lata and divides into its anterior and posterior branches which supply the lateral aspect of the thigh to a point just proximal to the knee (Fig. 1).

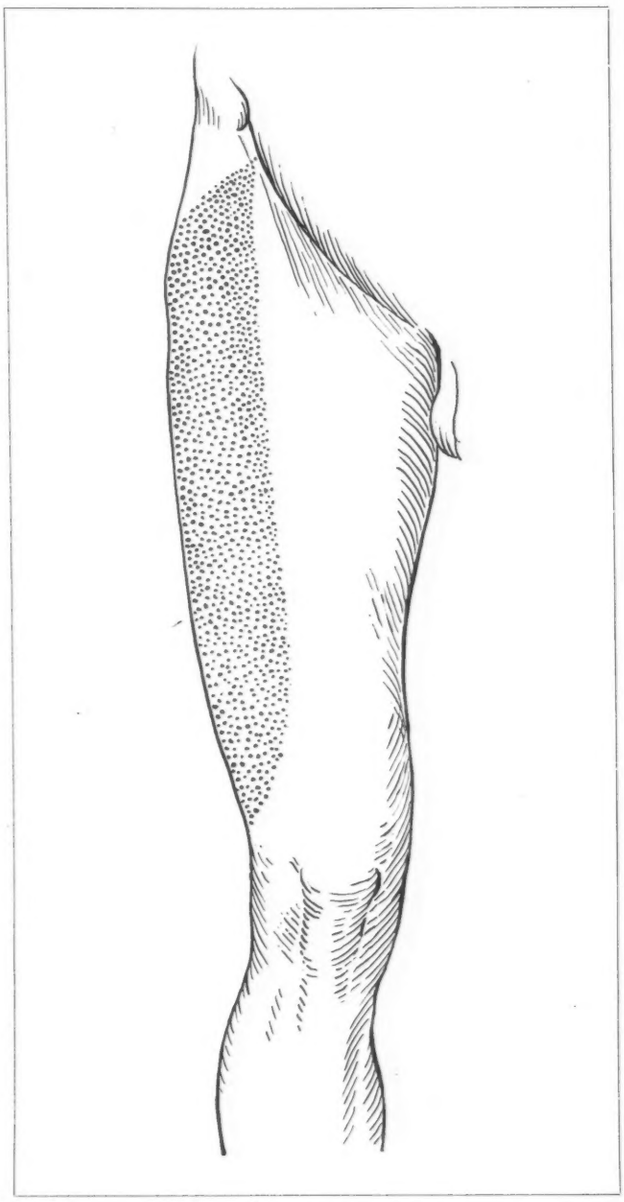

Fig. 1.—The sensory distribution of the lateral cutaneous nerve of the thigh.

*From the Department of Surgery, Hôtel-Dieu Hospital and Queen's University, Kingston, Ont.

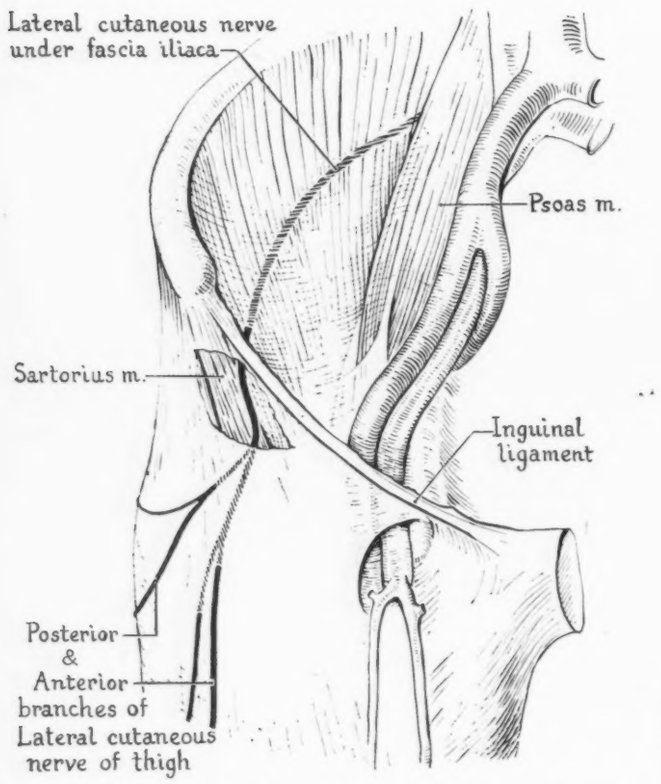

Fig. 2.—The normal anatomy of the lateral cutaneous nerve of the thigh.

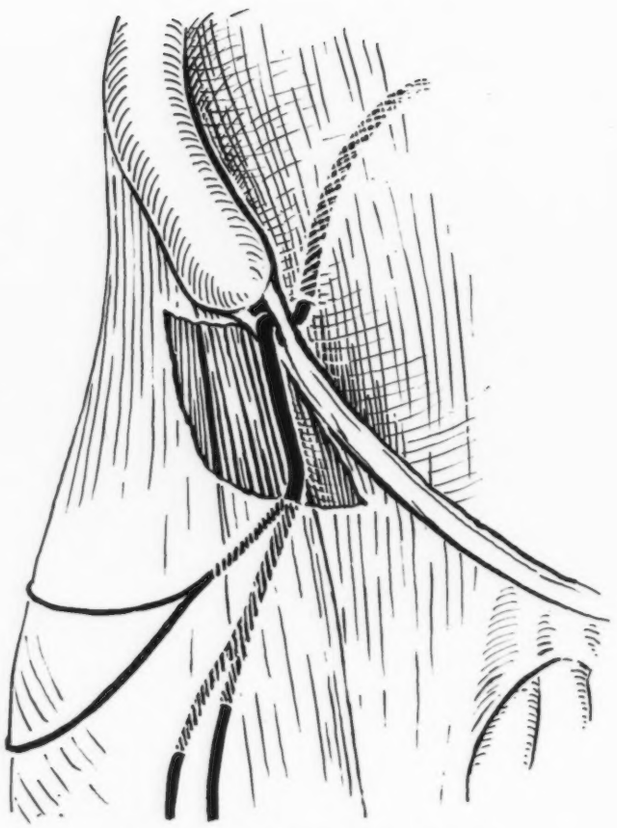

Fig. 3.—Meralgia paresthetica Type I.

ETIOLOGY OF MERALGIA PARESTHETICA

The etiology of the condition can be discussed under two headings: predisposing lesions and precipitating causes.

Predisposing Lesions

Since our original publication on this disease, we have had the opportunity of studying many more patients who presented the signs and symptoms of meralgia paresthetica. We now recognize four variants of the anatomical relationships in the thigh which may produce the classical picture of this disorder. This number may increase when an anatomical-surgical study of the area, now in progress, has been completed. The first anatomical variant is the classical split ligament, previously described, and depicted in Fig. 3. The second variant consists of a sharp ridge of iliacus fascia lying posterior to a normally placed nerve but causing a bow-string deformation of the nerve when the patient is in the supine position (Fig. 4). The third variant in the anatomy of this area occurs when the nerve enters the thigh in the substance of the sartorius muscle. On dissection, the nerve is found to enter the sartorius at the point of origin of the muscle from the anterior superior spine and it passes distally in the muscle for a distance of approximately 3 to 5 cm. before emerging beneath the fascia lata preparatory to its final distribution (Fig. 5). In the fourth variant, the lateral cutaneous nerve enters the thigh, crossing the iliac crest, lateral and posterior to the anterior superior spine, where a groove usually marks its passage. In this location, the nerve is

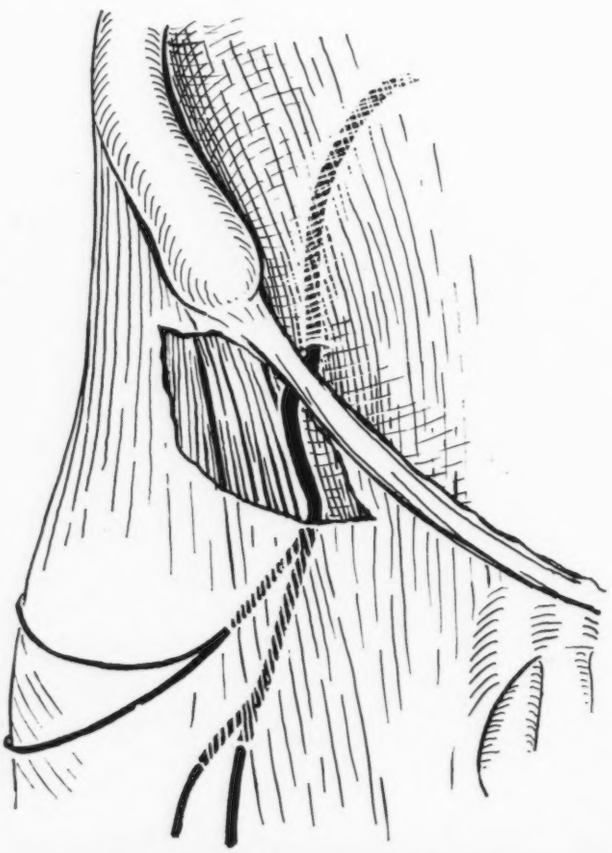

Fig. 4.—Meralgia paresthetica Type II.

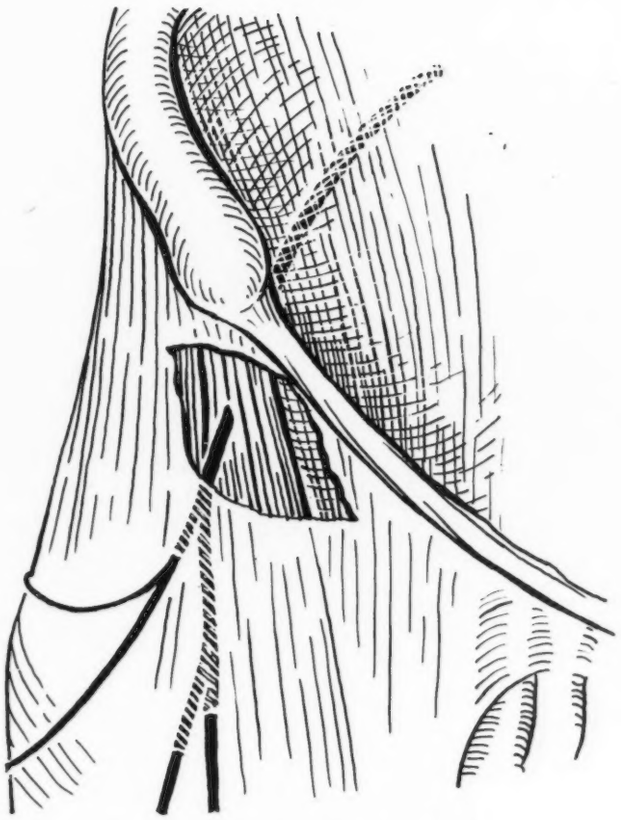

Fig. 5.—Meralgia paresthetica Type III.

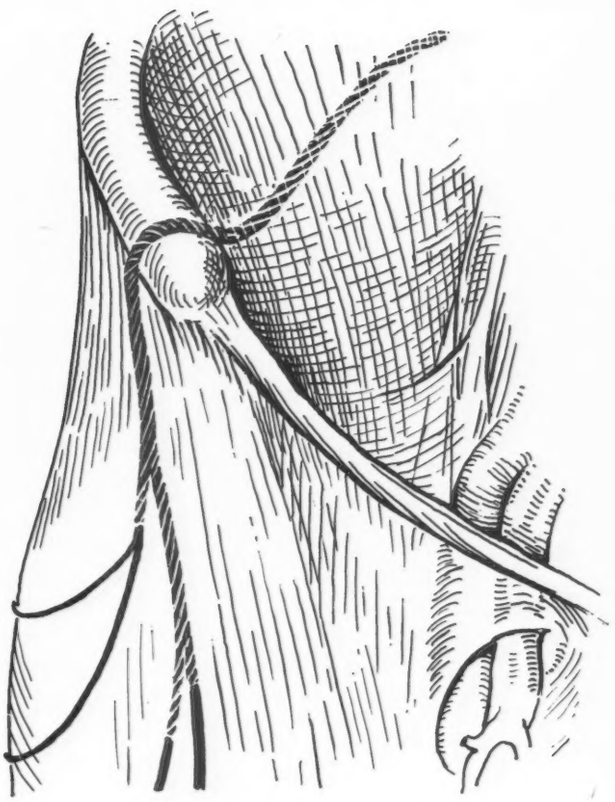

Fig. 6.—Meralgia paresthetica Type IV.

exposed to the pressure of encircling garments or belts (Fig. 6).

Precipitating Causes

These include obesity; the increased intra-abdominal pressure associated with pregnancy, ascites or tumour; the adoption of the recumbent position in debilitating disease, or after anesthesia or surgery; and altered mechanics of the hip joint secondary to intraspinal disease such as herniation of an intervertebral disc.

TREATMENT

The additions to anatomical knowledge of the area have necessitated a further division of treatment into conservative and operative; the appropriate type of treatment can be decided almost on the patient's history alone.

Conservative Treatment

When pain appears in the thigh following bed rest or anesthesia, it can usually be relieved by the local infiltration of the nerve with an anesthetic agent on one or two occasions. In pregnancy, unless the pain is completely incapacitating, conservative therapy should be employed; only rarely will the symptoms justify surgical intervention following delivery. However, if the pain is incapacitating during pregnancy, surgical treatment should be considered because of the simplicity of the operation and the great relief that it affords.

Operative Treatment

Patients who develop meralgia paresthetica while they are leading normally active lives seldom respond to conservative therapy; much time and suffering can be avoided if surgical exploration is carried out at once. At operation, the area is exposed through a transverse incision just below the anterior superior spine; the fascia lata is incised transversely, exposing the sartorius and the iliacus muscles. In Types I and II of the anatomical variants previously described, the nerve is identified between the iliacus and sartorius muscles and traced proximally to the inguinal ligament. In meralgia due to the variant Type I, the abnormal ligament is identified and the posterior band of the split ligament is completely incised, allowing the nerve to fall posteriorly (Fig. 7). In meralgia due to the variant Type II, the tight band of fascia iliaca is incised and a tunnel is made for the nerve in the substance of the iliac muscle itself (Fig. 8). If the nerve appears to have been damaged irreparably by pressure, it is wise to section the nerve above the level of the inguinal ligament. This will prevent the recurrence of symptoms due to the development of a traumatic neuroma in the area at a later date.

In meralgia due to the variants Type III and Type IV, the nerve will not be found in the normal anatomical position. A search is carried out lateral to the anterior superior spine, and if the nerve is found crossing the iliac crest (meralgia Type IV), it should be sectioned above this level. Anesthesia

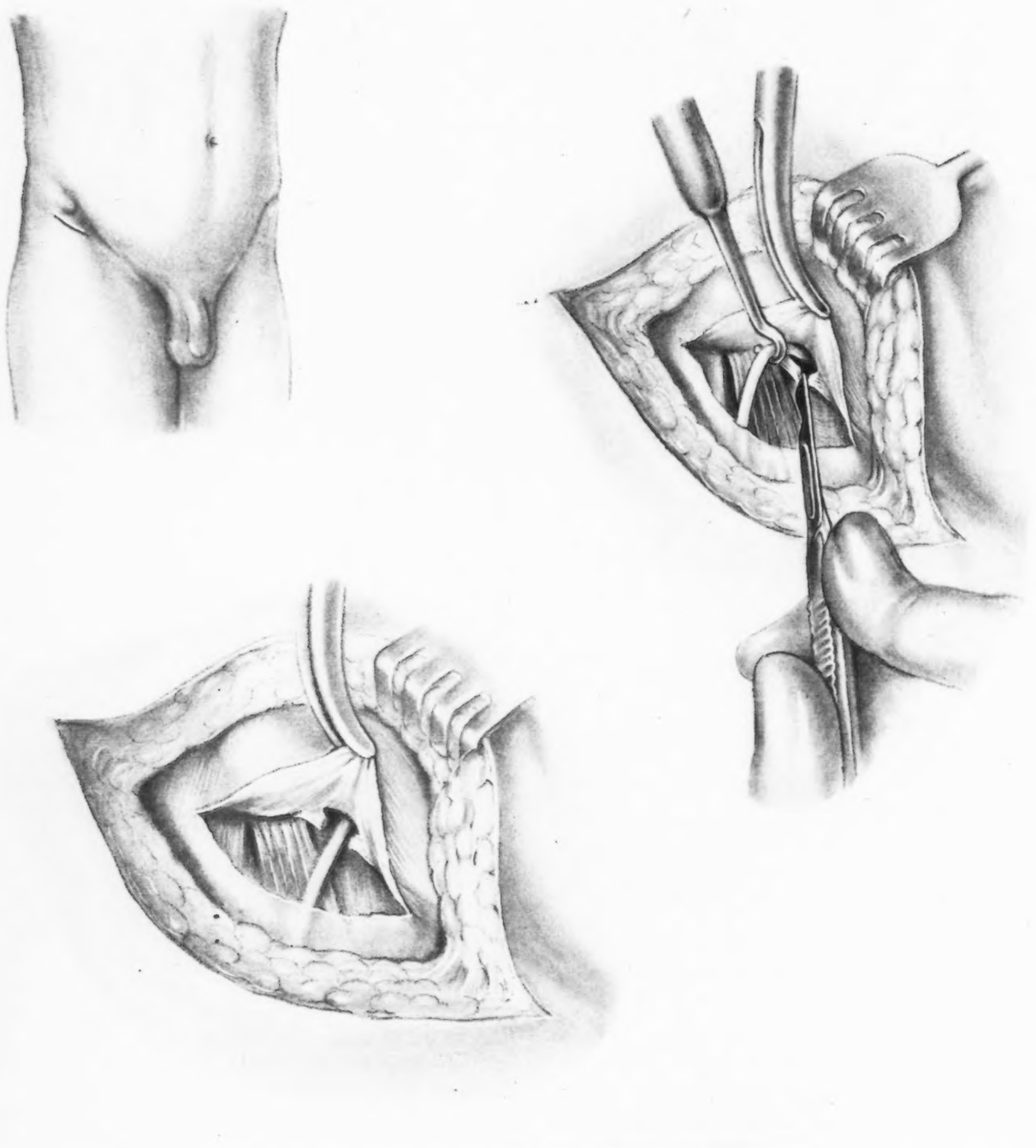

Fig. 7.—The operative treatment of meralgia paresthetica Type I.

will be permanent but the disability produced is minimal.

If, after careful search of the area, the nerve is still not identified, the existence of the third type of anatomical variant must be assumed. The sartorius muscle is sectioned transversely just distal to its origin; of necessity, this will section the nerve, and the proximal end of the nerve should be followed above the level of the anterior superior spine; a second section of the nerve is done at this level. Again, an anesthetic area will be produced.

DISCUSSION

Meralgia paresthetica remains a symptom complex that is as exotic as its name. It is not, however, a medical curiosity. It is common and it can be excruciatingly painful and incapacitating. This disease continues to be recognized late, if at all, and needless suffering is allowed to continue, the patient frequently being labelled as psychoneurotic, or even psychotic. One patient seen with symptoms from a Type III anatomical variant was sent for consultation as an alternative to admission to an institution for the mentally ill. She had had previ-

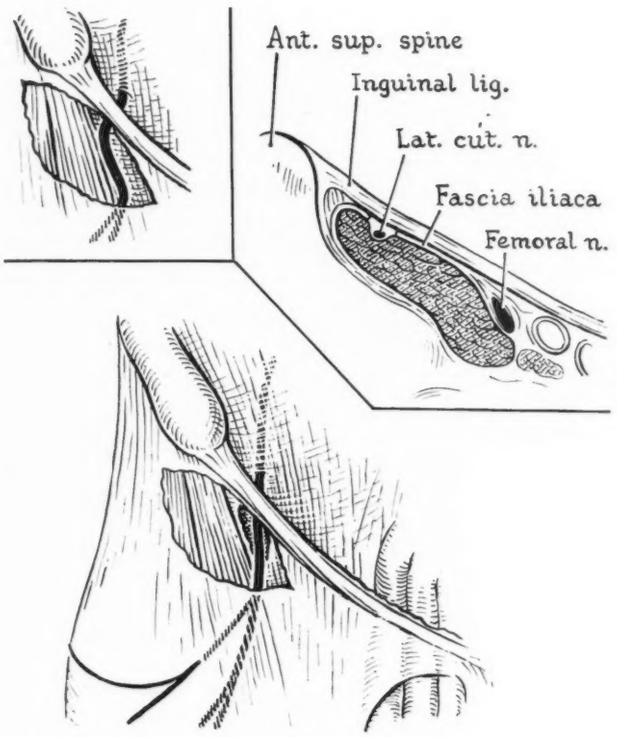

Fig. 8.—The operative treatment of meralgia paresthetica Type II.

ous exploration of the area on one occasion, with no improvement in symptoms. The results of muscle and nerve section in her case have been most gratifying.

Orthopedic surgeons have recognized the syndrome of pain in the distribution of the lateral cutaneous nerve of the thigh accompanying L4-5 or L5-S1 disc herniation; it was thought to be due to abnormal communications of the L1-L2 root complex with L4, L5 and S1. It seems more reasonable to assume that the spasm of the paravertebral musculature and consequent forward tilt of the pelvis is sufficient to cause a bowstring deformation of the lateral cutaneous nerve of the thigh and produce pain in its distribution.

SUMMARY

The subject of meralgia paresthetica is reviewed. The symptom complex can be divided into Types I, II, III, or IV, on the basis of the type of anatomical variant present. Meralgia paresthetica is not a rare disease, and it may be completely incapacitating. The conservative and operative treatments of this lesion are discussed.

I would like to thank Miss Janet Seaton for the excellent illustrations and her unfailing interest in the graphic reproduction of word pictures.

REFERENCES

1. GHENT, W. R.: *Canad. M. A. J.*, **81**: 631, 1959.
2. BERNHARDT, M.: *Neurol. Centralbl., Leipzig*, **14**: 242, 1895.
3. ROTH, V. K.: *Med. Obozr., Mosk.*, **43**: 678, 1895.

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VANILLIC DIETHYLAMIDE* IN THE MANAGEMENT OF ACUTE RESPIRATORY INSUFFICIENCY: A PRELIMINARY REPORT†

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THE occurrence of six cases of acute respiratory failure in the short span of a month at the Queen Mary Veterans' Hospital has prompted us to review our management of these cases. Our interest was further stimulated by the fact that we have been using a new respiratory stimulant, vanillic diethylamide,[1-3] in the treatment of patients with chronic respiratory disease. These six cases, therefore, furnished some basis for a preliminary evaluation of this compound in acute respiratory failure as well as for a review of other methods of treatment of this emergency.

Treatment of acute respiratory failure with hypoxemia, hypercapnia and acidosis, in the form in which it occurs in chronic lung disease such as obstructive emphysema, involves the management of factors such as respiratory infection, airway obstruction, heart failure and respiratory centre depression, all of which may combine to precipitate the alveolar hypoventilation which underlies the disorder. The liberal use of antibiotics and bronchodilators, digitalis, diuretics and occasionally adrenal steroids may be indicated in the therapeutic program, but may by themselves prove to be inadequate. Previous reports[4, 5] have demonstrated that the removal of tracheal secretions by tracheotomy and the maintenance of adequate ventilation by mechanical respirators are of paramount importance and may be life-saving when other measures have failed. Such reports have mentioned, but perhaps at times without sufficient stress, the meticulous and constant supervision and care which are necessary when these measures are added to the therapeutic regimen. Even with very careful supervision a significant number of patients with emphysema, amounting to some 30% according to published reports, do not survive these acute episodes.[5] This points up the difficulty of management of these cases, even when all the known factors, including ventilation, are well controlled.

Since respiratory centre depression is one of the factors involved, as well as total cerebral depression, it seemed worth while to study the effects of a respiratory centre stimulant and analeptic in addition to those of other measures in the manage-

*Supplied as Emivan by the U.S. Vitamin and Pharmaceutical Corporation.

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ment of these cases. The use of respiratory centre stimulants is not new. Nikethamide, alpha-lobeline and other drugs have been employed in the past to stimulate respiration.[6] Their effects have, however, been so widespread over the whole central nervous system or on other parts of the body such as the heart and circulation in general that they have fallen into disuse in many centres as therapeutic agents for this particular syndrome. Since vanillic diethylamide is thought to have a more selective effect on the respiratory centre than other compounds and since it has been reported to have a greater margin of therapeutic safety, it was felt that its administration to patients with acute respiratory failure could be of value.

During the month between February 21 and March 24, 1961, six cases of respiratory acidosis in patients with emphysema were seen at the Queen Mary Veterans' Hospital, and case reports of these six will be presented. Various combinations of the aforementioned modes of therapy were utilized in these patients, as well as vanillic diethylamide.

The basis of therapy in all except one of the patients was early tracheotomy with insertion of a cuffed Jackson tube through which frequent aspiration of sections was carried out and mechanical assistance to ventilation applied using either a pressure-cycled machine of the Bird type or a volume-cycled apparatus of the Engström type. A 40% mixture of oxygen and air was usually used with the respirator. In addition, a nebulized bronchodilator, usually isoproterenol, was given at hourly intervals during the acute stages, together with intravenous aminophylline either as a continuous infusion or intermittently. Large doses of penicillin, four or more million units daily, were used, frequently together with chloramphenicol. Digitalis and diuretics were administered when signs of heart failure were present. Oral feeding was avoided, in general, during the acute stages, and hydration and nutrition were maintained by intravenous administration of fluids and electrolytes or by Levin tube feedings. An attempt was made to avoid respiratory centre depression by the administration of sedatives, but these were used on two occasions for specific indications. Vanillic diethylamide in the intravenous form was given either as a continuous infusion in varying concentrations and at varying rates depending on the state of consciousness of the patient or in intermittent, moderately rapid injections. When the intravenous route appeared to be no longer necessary, the oral route was sometimes substituted in a dose of 40-60 mg. four times daily.

Besides observation of the clinical condition, especially the state of consciousness, the patient's course was followed by measurement of pH, pCO_2 and the standard bicarbonate of arterial blood on an Astrup pH meter. Determinations of oxygen saturation were made in some cases both with a Waters Conley ear oximeter and the Van Slyke apparatus.

CASE REPORTS

CASE 1.—A.G.M., a 50-year-old male clerical worker, gave a history of chronic cough dating back to 1948, with shortness of breath on exertion. In August 1960, increased dyspnea, of which he was complaining, was thought to be part of a hyperventilation syndrome, and re-breathing into a paper bag was recommended. In January 1961, management of a severe psychoneurotic disorder necessitated giving him a light job at a domiciliary care hospital; sedatives and tranquillizers were also part of his treatment. On February 1, 1961, he was hospitalized with a fever of 101° F. and increased dyspnea. Examination of his chest revealed bilateral basal inspiratory rales, though a chest radiograph was normal. His dyspnea became progressively worse and by February 20, 1961, he was described as being in "status asthmaticus". He was given morphine, 1/6 grain intravenously, aminophylline, antibiotics and oxygen by mask, as well as intravenous hydrocortisone. On the morning of February 21, 1961, with his state of consciousness already impaired, he was given 2 grains of sodium amobarbital intravenously and lapsed into coma.

On admission to the Queen Mary Veterans' Hospital at 4.00 p.m. on February 21, 1961, he was found comatose, markedly cyanotic and breathing rapidly, shallowly and ineffectively. His temperature was 101° F., blood pressure 90/45 mm. Hg and pulse rate 124/min. Some jugular venous distension was noted, and on auscultation of the chest there were diffuse expiratory rhonchi and basal inspiratory rales. The liver edge was palpated four fingerbreadths subcostally, but there was no peripheral edema. The conjunctivae were suffused and chemotic.

A tracheotomy was performed immediately with insertion of a cuffed Jackson tube, and he was started on a pressure-cycled mechanical respirator, and frequent suctioning of the tracheobronchial secretions was instituted. He remained comatose and cyanotic, and arterial blood gas studies at 7.00 p.m. revealed a pH of 7.08, a pCO_2 of 122 mm. Hg and a standard bicarbonate of 32 mM./l. His therapeutic regimen was at this point augmented by antibiotics in large doses, intravenous aminophylline in a continuous infusion and nebulized isoproterenol at hourly intervals. Also a continuous infusion of vanillic diethylamide was started in a concentration of 1 g. per 200 c.c., run in at 30 drops per minute. On this combined therapy, the patient became at least partially rousable, and a repeat arterial pCO_2 at 11.00 p.m. (see Fig. 1) showed a significant drop. By 9.00 a.m. the next morning he had received 3 g. of vanillic diethylamide in the above fashion but was still comatose. A further 100 mg. of the drug was injected rapidly by the intravenous route at this time. There was an immediate increase in frequency and depth of respiration, and within a minute the patient was restored to consciousness and was able to answer questions rationally. A repeat determination of arterial pCO_2 revealed a marked drop to 62 mm. Hg and a return of arterial pH to within normal limits. He relapsed to a somewhat drowsy state during the day and was given a series of moderately rapid intravenous injections of 100 mg. of vanillic diethylamide at approximately hourly intervals. By the third day he was normally alert and remained so thereafter. A rise in arterial pCO_2 accompanied by a marked rise of bicarbonate observed on the third day of treatment was possibly a response to temporary interruption of bronchodilators and respirator therapy or to tracheobron-

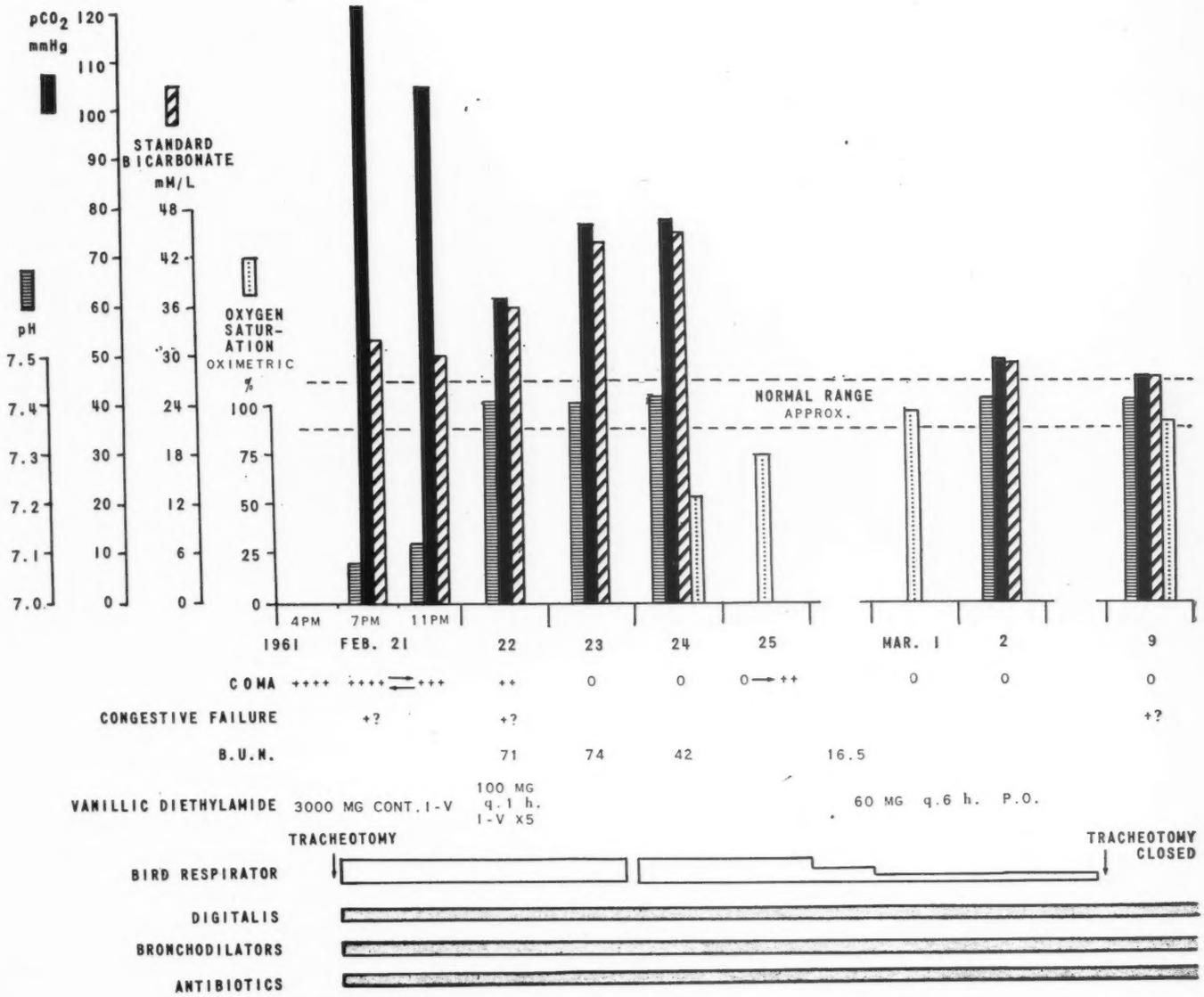

Fig. 1.—Case 1. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. Note the extremely high pCO_2 and low pH values at the outset. The effect of vanillic diethylamide as an adjunct to other therapy is indicated by the shift of abnormal values to normal while it was being used and by the rise in pCO_2 when its use was discontinued on February 23, 1961.

chial obstruction due to the accumulation of tracheal secretions. Subsequently the pCO_2 and bicarbonate levels dropped gradually toward normal levels concomitantly with a rise in oxygen saturation (determined by an ear oximeter while the patient was no longer using the respirator) to normal levels.

Admission laboratory studies revealed a hemoglobin value of 12.5 g. %, a hematocrit of 40% and a leukocyte count of 20,200 per c.mm. The blood urea nitrogen (BUN) level was elevated on admission to 71 mg. % and the serum potassium to 6.25 mEq./l.; the chloride value was 94.1 mEq./l. These abnormalities later disappeared. An electrocardiogram revealed auricular tachycardia, and chest radiographs were reported as showing hyperaeration, flat diaphragms and a prominent left hilar shadow.

It was found possible to discontinue respirator therapy and close the tracheal stoma on the 16th day of therapy. At this time the patient still complained of some dyspnea and was seen to be mildly cyanotic. The anteroposterior diameter of his chest was increased. Expansion was reduced and he had diffuse rhonchi on forced expiration, hyperresonance and poor air entry, with a few inspiratory rales at the lung bases posteriorly. This clinical picture and the results of pulmonary function tests which showed reduced vital capacity, increased residual and functional residual volumes, reduced expiratory flow rates and a markedly reduced diffusing capacity for carbon monoxide suggested the diagnosis of emphysema.

Comment.—This case illustrates the kind of care necessary in the treatment of patients with pulmonary emphysema who may be on the verge of acute respiratory insufficiency. The two factors which apparently caused this patient to enter a state of CO_2 narcosis were the respiratory infection and the ill-advised use of sedatives, especially the intravenous sodium amobarbital, at a time when his consciousness was already impaired.

The institution of tracheotomy and assisted ventilation undoubtedly did much towards lowering his

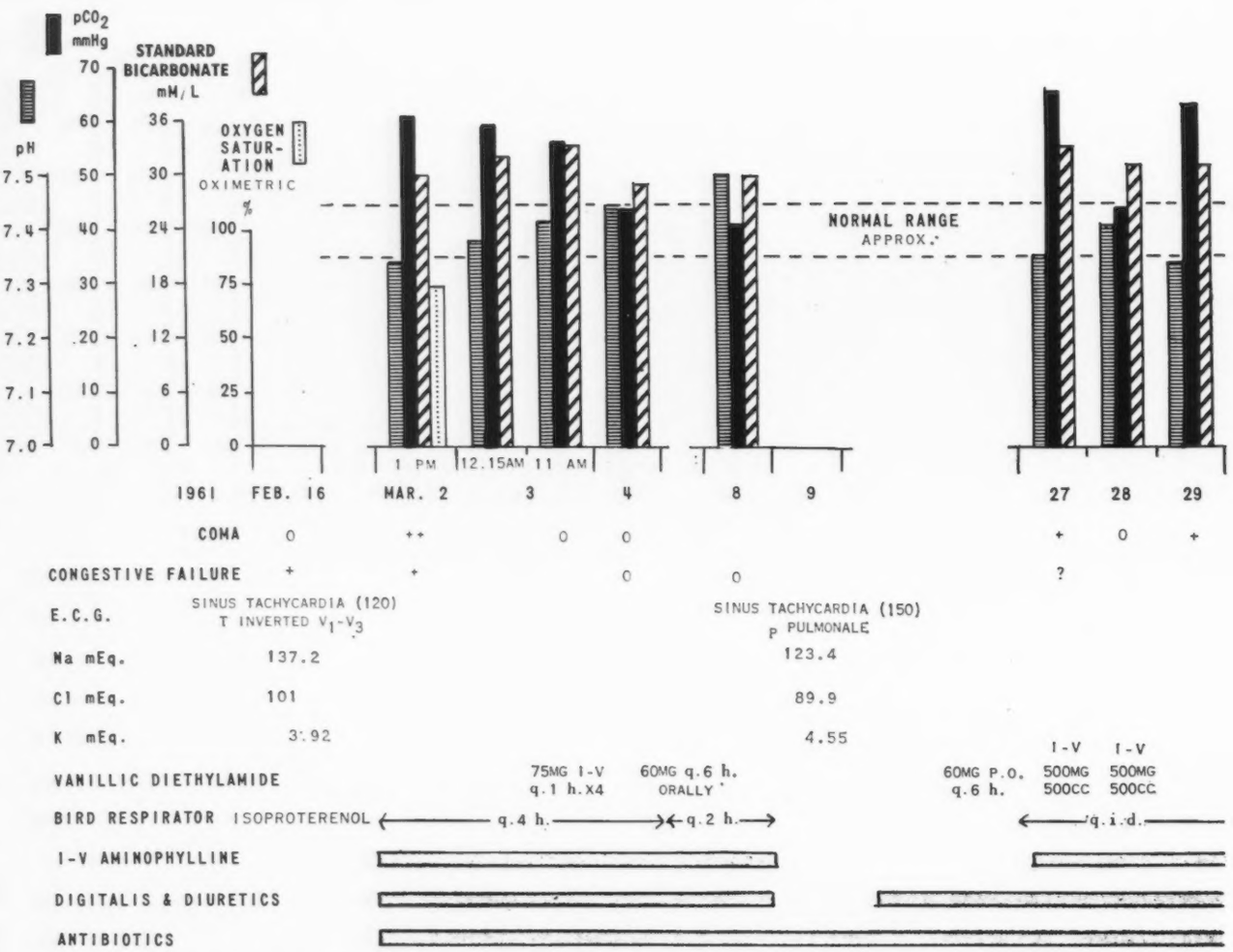

Fig. 2.—Case 2. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart shows how the abnormal values can be corrected by adequate multiple therapy and how they can revert to abnormal values when therapeutic efforts are lessened or discontinued.

pCO_2 values from the high level of 122 mm. Hg. The intravenous drip of vanillic diethylamide apparently contributed to this improvement. The dramatic response to the rapid intravenous injection of a further 100 mg. at 9:00 a.m. was probably due to the fact that the patient was fairly close to the level of consciousness at this time. Although the injection undoubtedly stimulated respiration greatly, as evidence by the patient's chest movements, the return to consciousness in such a short time was probably due to a general analeptic effect rather than an effect solely on the respiratory centre.

CASE 2.—D.B.J., a 68-year-old retired carpenter, was admitted to the Queen Mary Veterans' Hospital on February 12, 1961, complaining of severe shortness of breath and cough. There had been repeated admissions to hospital since he stopped work in 1955, for exacerbations of chronic bronchitis and emphysema, and he gave a history of cough and paroxysmal wheezing dyspnea since 1917.

On examination he was acutely dyspneic and cyanotic. He had clubbed fingers; his chest was barrel-shaped, moved poorly and was hyperresonant to percussion. There were diffuse expiratory rhonchi on auscultation. Some signs of right-sided heart failure were present. His hemoglobin value was 17.1 g. %, hematocrit 54%, and leukocyte count 18,700 per c.mm. Sputum culture revealed a heavy growth of *H. influenzae*. An electrocardiogram showed auricular fibrillation. The chest roentgenogram revealed low flat diaphragms, honeycombing at both bases suggesting bronchiectasis, and prominent hilar shadows.

After digitalization and administration of diuretics there was some transient improvement. He became less breathless, and sinus rhythm was seen to be restored on a subsequent electrocardiogram. On February 24, 1961, the patient developed a fever of 101° F., and a repeat chest radiograph revealed an infiltration in the right mid-lung field. The patient was placed on antibiotics and intravenous aminophylline was given, but the fever persisted, and on March 2, 1961, he was noted to be extremely drowsy, markedly cyanotic and tachypneic. There was a suggestion of flapping tremor, and mild ankle edema was noted. The oxygen saturation (oximetric) value was 74%; arterial blood pH, 7.34; pCO_2, 61 mm. Hg, and standard bicarbonate 30 mM/l. More intensive antibiotic therapy was instituted and he was given diuretics, a continuous intravenous infusion of aminophylline and nebulized isoproterenol delivered by means of the Bird respirator at four-hour intervals. In addition, meprobamate, which he had been receiving, was discontinued. With this program there

was some clinical improvement, in terms of increased alertness, but a repeat arterial pCO_2 determination the next day showed little change. He was accordingly given a series of four intravenous injections of 75 mg. of vanillic diethylamide at hourly intervals. The next day his mental state was quite clear, and his arterial pCO_2 had fallen to 44 mm. Hg. His course subsequently was without incident until March 7, 1961, when, because of apparent clinical deterioration, he was given an extra dose of digitalis, and isoproterenol treatments, using the Bird respirator, were increased to two-hourly intervals. On March 8, 1961, he was found to be weak, dyspneic and ashen in colour, and his heart rate was 144/min. An ECG revealed sinus tachycardia and signs suggesting cor pulmonale; electrolyte studies revealed low sodium and chloride levels, and the arterial pCO_2 was found to be 41 mm. Hg with a pH of 7.5 and a standard bicarbonate concentration of 30 mM./l. Use of diuretics and the Bird respirator was stopped; digitalis was temporarily discontinued; he was given a diet without sodium restriction, and subsequently improved.

The improvement in this mild case of respiratory acidosis was short-lived, despite the administration of oral vanillic diethylamide in a dosage of 240 mg. daily. On March 27, 1961, he was again noted to be drowsy, and repeat arterial blood gas studies once more showed an elevated pCO_2 of 66 mm. Hg. It was observed, in addition, that his weight had increased by 11 lb. He was restarted on a diuretic and sodium restriction, as well as on nebulized isoproterenol delivered by the Bird respirator. In addition an infusion of 500 mg. of vanillic diethylamide combined with 7½ grains of aminophylline in 500 c.c. of 5% glucose in water was administered daily for two days. As can be seen in Fig. 2, some very brief improvement was obtained.

Comment.—This patient was recognized to be in acute respiratory insufficiency with hypercapnia due apparently to a combination of pneumonia and right heart failure. It is possible that the meprobamate which he had been receiving contributed to the acute respiratory failure. Measures to control these factors, together with increased mechanical ventilation and the respiratory stimulation of vanillic diethylamide, were sufficient to restore the arterial blood values to normal. It should be noted that in this relatively mild case tracheotomy was not necessary to reduce the respiratory dead space. Since the patient was sufficiently conscious to cough and expectorate, tracheostomy was also not necessary to remove excess tracheobronchial secretions.

It should also be noted that, in spite of oral therapy with vanillic diethylamide, increased cardiac decompensation caused him to revert to a hypercapnic state, which was again readily corrected by the use of a combination of intravenous therapy with the same drug, assisted respiration, diuretics and sodium restriction.

CASE 3.—J.A.R., a 63-year-old man, was admitted to the Queen Mary Veterans' Hospital on March 9, 1961, complaining of shortness of breath on exertion, orthopnea and a mild cough. He had a history of chronic cough since 1942, and previous episodes of confusion and sleepiness were recorded, once with a bout of lobar pneumonia. On examination he was noted to have distended external jugular veins, an increased anteroposterior diameter of the chest, with poor chest movement, and bilateral basal inspiratory rales. Marked edema of the lower extremities was also present.

His hemoglobin value was 12.9 g. % and hematocrit 43%. Chest radiographs were reported as showing cardiomegaly and pulmonary congestion. An electrocardiogram revealed right-axis deviation and clockwise rotation, and was considered characteristic of pulmonary disease with emphysema.

The patient was started on treatment for heart failure, and a bedtime sedative of 1½ grains of phenobarbital was also ordered. On the morning of March 13, 1961, he was reported to be confused and cyanotic, and at noon of the same day was found comatose and pulseless. Cyanosis was markedly increased and there were long periods of apnea. Intravenous injections of vanillic diethylamide and nikethamide, together with manual artificial respiration, improved his respiration, and further improvement resulted from the use of the Bird respirator applied with a mask, to the point where the patient returned to a confused state of consciousness. At this stage he was still cyanosed and unequal pupils were noted; the right pupil was dilated and nonreactive. Arterial blood gas studies revealed a pH of 7.20, pCO_2 of 66 mm. Hg and a standard bicarbonate value of 23 mM./l. A tracheotomy was performed, and the patient was continued on mechanical ventilation with the Bird respirator. Frequent suctioning of secretions was performed, and antibiotics and bronchodilators were given. By 10.00 p.m. the same evening a normal state of consciousness had been restored, and the pupillary inequality had disappeared; these changes were preceded by a drop in arterial pCO_2 to 52 mm. Hg.

On the second day of treatment there was a return of anisocoria and confusion, and a marked leak of air was noted through the mouth, all of which were associated with a rise in arterial pCO_2 to 60 mm. Hg (see Fig. 3). Re-inspection of the tracheotomy revealed that only the terminal portion of the Jackson tube was inserted into a largely intrathoracic trachea and that the rubber cuff was lying outside the trachea. Substitution of a long rubber endotracheal tube improved the patient's condition and the patient's subsequent course and recovery was uneventful. The tracheal stoma was closed and assisted respiration was discontinued on March 28, 1961.

Comment.—In this patient with emphysema the impetus to CO_2 narcosis was apparently provided by a combination of right heart failure, probable tracheobronchial infection and night-time sedation. Although some improvement was noted without the use of a tracheotomy, the accumulation of tracheobronchial secretions which could not be cleared by cough and expectoration made this procedure necessary.

The case does illustrate, however, the extreme care which must be exercised in watching such patients once the tracheotomy has been established.

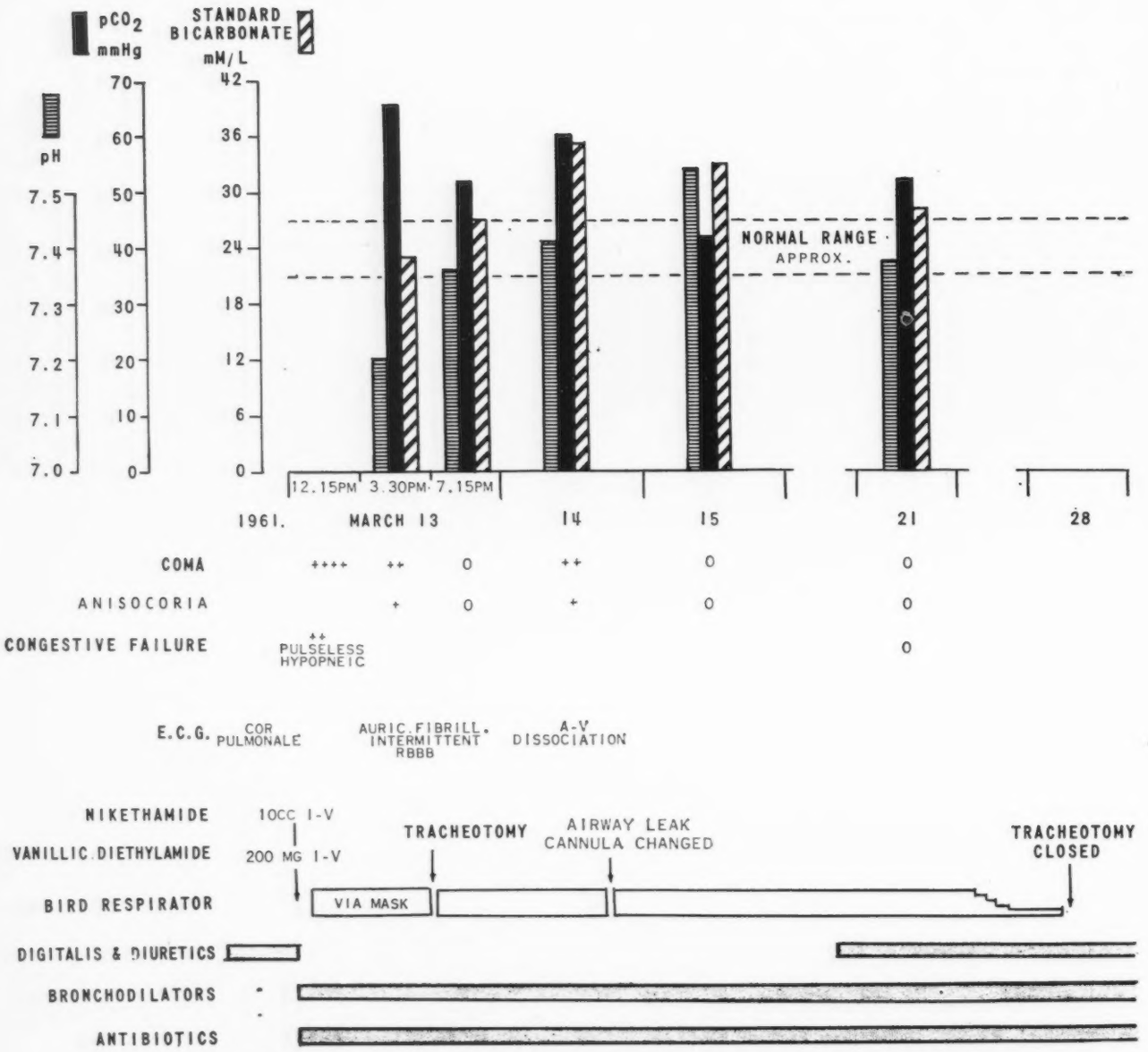

Fig. 3.—Case 3. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart indicates how rapidly a patient may sometimes come out of coma and how inefficient ventilation may tend to return the patient to this condition, as occurred on March 14, 1961.

A leak in the airway or obstruction in the tubes must be recognized and corrected immediately or they will nullify the whole procedure and cause a relapse.

CASE 4.—J.L.L., a retired clothing salesman, aged 71, had had previous admissions to hospital for management of symptoms of emphysema associated with cor pulmonale and congestive failure. He dated the onset of respiratory symptoms to 1951, but admitted to having had "a weak chest" since childhood, with frequent colds which went to his chest. During an admission dating from November 29 to December 23, 1960, arterial blood gas studies (Van Slyke) revealed an oxygen saturation of 89% and a CO_2 content of 39.45 volumes %.

He was readmitted to hospital on February 16, 1961, after a period without digitalis, in a state of severe dyspnea with signs of right-sided failure and radiological evidence of cardiomegaly. He was not cyanotic; his chest was hyperinflated and hyperresonant with little movement, poor air entry and no adventitious signs. The hemoglobin value was 17.1 g. % and hematocrit 52%. An ECG showed sinus tachycardia, p-pulmonale and right-axis deviation.

Administration of digitalis and diuretics as well as steroids and bronchodilators relieved the signs of heart failure but left him as severely dyspneic as before. On March 14, 1961, after one month in hospital, coincidentally with a rise in his temperature to 102° F., he lapsed into a confused drowsy state with increased dyspnea and inspiratory rales at the right lung base, suggesting the presence of pneumonia. The arterial pCO_2 was found to be 70 mm. Hg; pH, 7.38, and a standard bicarbonate 38 mM./l. The administration of aminophylline intravenously and an intravenous infusion of vanillic diethylamide containing 1000 mg. in 500 c.c. run in at 20 drops/min., with assistance to respiration provided by the Bird machine through

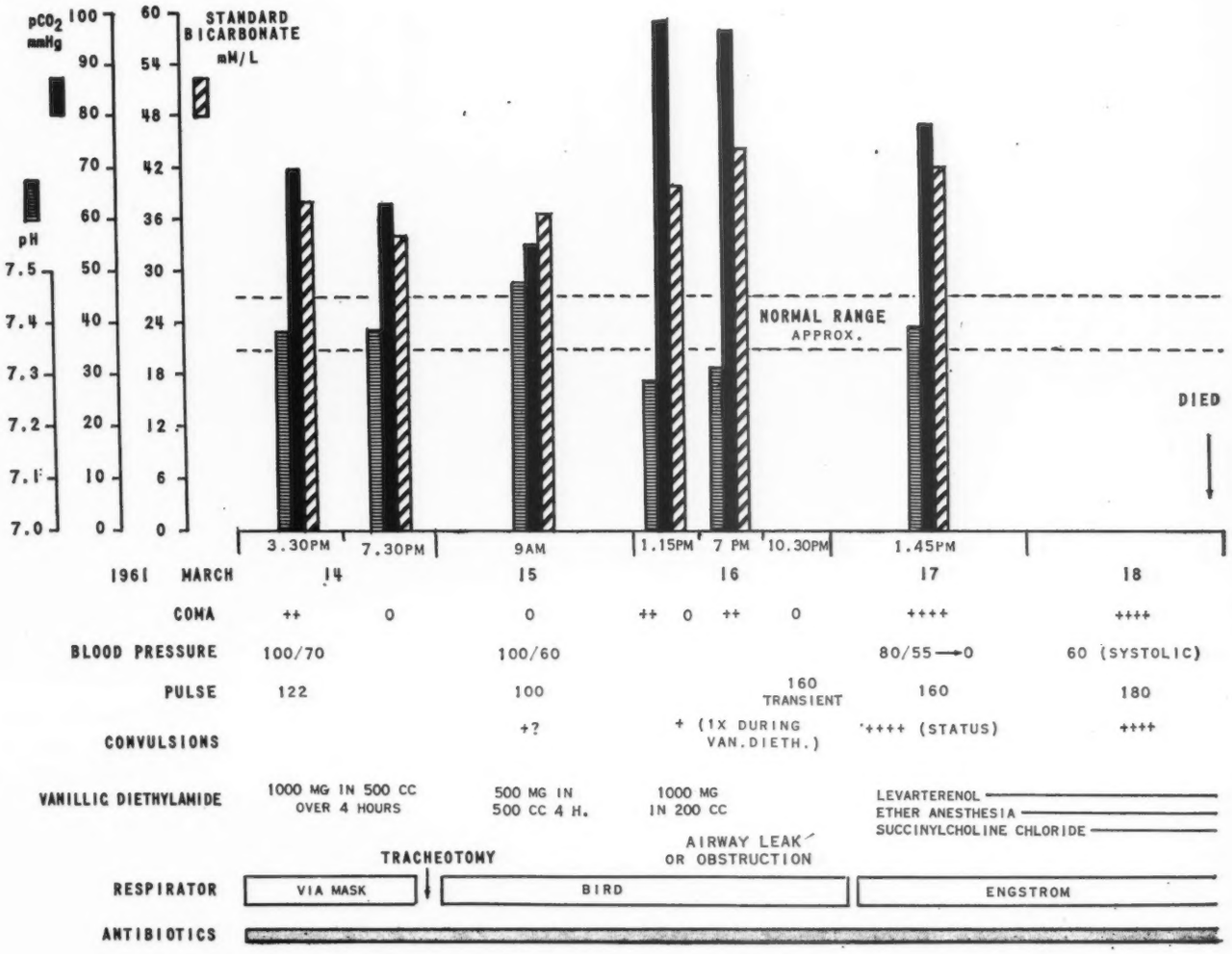

Fig. 4.—Case 4. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart illustrates the difficulties in management which may occur with some patients where irreversible brain damage due to anoxemia may occur. It is to be noted that the arterial pH had returned to normal but coma persisted.

a mask (which the patient tolerated poorly), resulted in a return to a normal state of consciousness and a drop in arterial pCO_2 to 63 mm. Hg. It was decided nevertheless to proceed with tracheotomy and mechanical ventilation with the Bird respirator applied through the tracheal stoma. Antibiotics and bronchodilators were also given. Despite the persistence of fever, on the second day of treatment he was normally alert and his pCO_2 had fallen to 55 mm. Hg. The next day, however, coincident with periods of leaking of air through the mouth (corrected by reinflating the rubber cuff), he became intermittently drowsy and confused again. Reassessment of the arterial blood gases revealed a pCO_2 of 98 mm. Hg, a drop in pH to 7.28, and a rise in the bicarbonate level to 41 mM./l. Intravenous vanillic diethylamide and reinflation of the cuff were only temporarily beneficial, and a recheck of the arterial pCO_2 value the same day showed no change. Furthermore, discontinuation of the respiratory stimulant was felt to be indicated, after a major seizure occurred followed by a period of tachycardia and marked hyperpnea.

Though his arterial pCO_2 was significantly lower the next day, his clinical condition had in fact deteriorated, a turn of events preceded by a period of cyanosis in the course of which it was found that the cuff of the tracheal cannula had slipped over the end of the cannula, obstructing the airway. Despite correction of this, the patient became increasingly drowsy, lapsing finally into a state of coma. Circulatory failure ensued, together with severe bronchospasm and generalized convulsions proceeding to status epilepticus. In spite of changing to an Engstrom respirator, and the use of intravenous hydrocortisone, ether anesthesia, intravenous succinylcholine chloride, diphenylhydantoin sodium, sodium phenobarbital (Luminal) and levarterenol, the patient died the next day, March 18, 1961.

At autopsy, marked emphysematous changes were found in the lungs associated with a marked degree of pulmonary congestion and edema, and right ventricular hypertrophy and dilatation; permission to examine the brain was not obtained. Details of the case are summarized in Fig. 4.

Comment.—In this patient hypercapnia was precipitated by a respiratory infection. The situation seemed to be moderately well controlled by the use of the measures initially instituted, since there was a return to consciousness and a drop in pCO_2. It is possible that, as in Case 2, these measures would have been sufficient had the patient been able to tolerate the oxygen mask. Since he had marked difficulties with this apparatus, a tracheotomy became necessary.

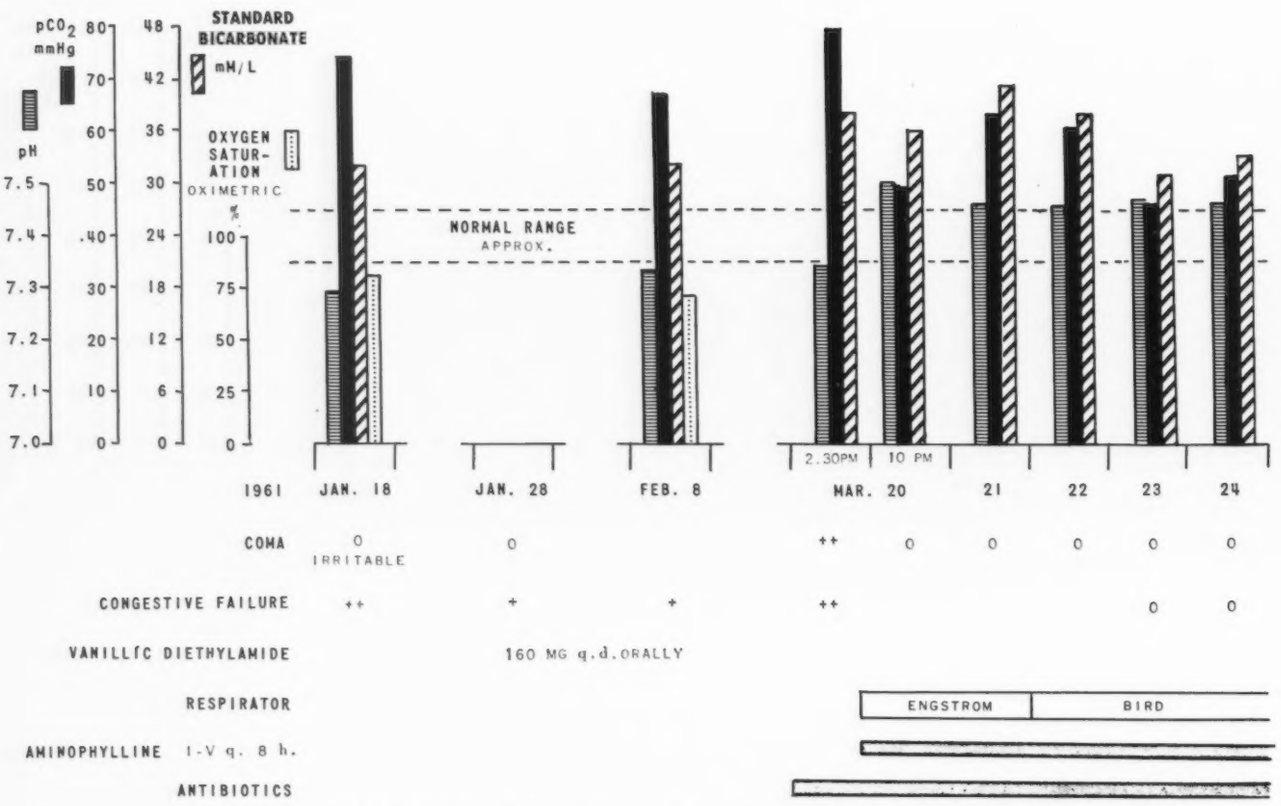

Fig. 5.—Case 5. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart illustrates the return to normal if satisfactory ventilation is established. It is possible that if continuous intravenous, instead of oral, vanillic diethylamide had been used, tracheotomy and ventilator therapy might have been avoided.

As in Case 3, the meticulous care necessary in watching for leaks in the airways is emphasized.

This patient also experienced convulsive seizures which were probably due to anoxemia. Since vanillic diethylamide may also cause cerebral irritation superimposed on that caused by the anoxemia, it was felt that this drug should be discontinued, which was done two days before his death. Further experience in its use may act as a guide in future cases of apparently irreversible cerebral changes due to anoxemia. The autopsy permission for examination of the brain was refused. This was unfortunate, since it might have helped in deciding what was the true cause of the failure to respond in this particular case. Since the convulsions had been present prior to the use of intravenous vanillic diethylamide and since the effect of this drug administered intravenously is very temporary, it is likely that the continued convulsions were due to either anoxemia or some other cerebral cause and not the drug itself.

CASE 5.—A.G., a 64-year-old man, had been diagnosed in previous admissions as having chronic bronchitis and emphysema with cor pulmonale and heart failure. He had a history of cough and wheezing dyspnea since his army service during World War I (1915). Arterial blood gas studies made on January 18, 1961, in the course of a prolonged admission to the Queen Mary Veterans' Hospital with congestive failure, revealed an oxygen saturation value of 81% and a CO_2 content of 54.2 vol. % (Van Slyke), with a pCO_2 of 74 mm. Hg, a pH of 7.29 and a standard bicarbonate of 32 mM./l. There was, at this time, no impairment of consciousness, though the patient was irritable. A 12-day trial of oral vanillic diethylamide in a dosage of 160 mg. daily produced little change in these values. The patient remained severely dyspneic and incapacitated despite treatment for heart failure and use of antibiotics and bronchodilators; he refused to go to a convalescent hospital for the remainder of the winter and was eventually released from the Queen Mary Veterans' Hospital on March 16, 1961.

He was readmitted three days later with a temperature of 102.4° F., drowsy, dyspneic and cyanosed, and complaining of being unable to cough up sputum. Signs of right-sided heart failure were present. He was treated by administration of digitalis, diuretics, antibiotics and bronchodilators, but his condition deteriorated. The next day, March 20, 1961, he was markedly drowsy, confused and had a flapping tremor of the hands. Arterial blood gas studies revealed a pCO_2 of 79 mm. Hg, a pH of 7.34 and a bicarbonate of 38 mM./l. A tracheotomy was performed without further delay, and the patient was started on the Engstrom respirator, intravenous aminophylline and antibiotics being continued. Rapid restoration of a normal state of consciousness, in this case, was associated with a more gradual lowering of arterial pCO_2 levels towards normal (see Fig. 5) and with persistence of muscle twitching and the flapping tremor despite normal or near normal levels of arterial pCO_2. During the first two days meperidine was required to sedate the patient, who was resisting the respirator. In addition, there was some initial difficulty with the airway; a leakage of air required correction by reinflation of

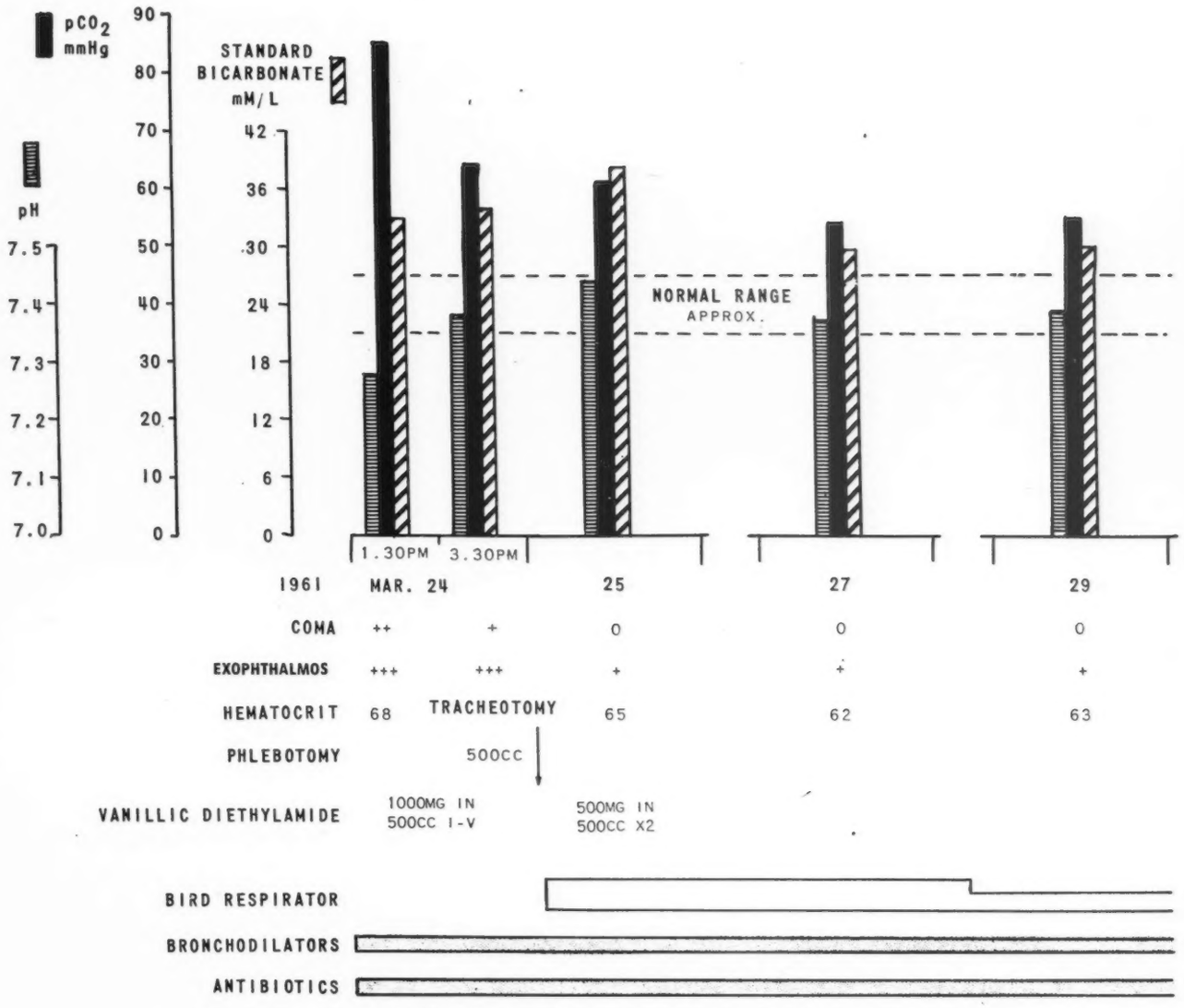

Fig. 6.—Case 6. Arterial blood gas values and summary of clinical course and therapy. Degrees of coma: 0 = none; + = dullness, mild drowsiness; ++ = marked drowsiness, confusion; +++ = stupor; ++++ = coma. This chart illustrates a satisfactory return of blood values toward normal ranges with the continuation of therapeutic agents used.

the cuff, as well as by a change of tube. His clinical course was, however, unaffected by these factors, and it was possible by March 22, 1961, to substitute the Bird respirator for the Engstrom machine and by March 27, 1961, to begin gradual discontinuance of assisted respiration.

Comment.—This patient had shown little response to oral vanillic diethylamide used for his chronic symptoms. The contrast between this and the usual response to intravenous therapy with the same drug for acute cases may have been due to lack of absorption of the enteric-coated tablets which we were using at that time. It may also have been due to a difference in response between the chronic symptoms and the acute respiratory failure syndrome superimposed on chronic pulmonary disease.

As in some of the previous cases, an acute episode of hypercapnia was produced by a respiratory infection complicated by right heart failure.

Muscle twitchings and other signs of cerebral irritation were present in this patient, as were general restlessness and a tendency to "fight" the respirator. It has been noted in commenting on some of the previous cases that sedation may be one of the factors involved in precipitating CO_2 narcosis. In this particular case sedation was used, but it should be emphasized that this was done only when ventilation could be controlled mechanically in the sedated patient. When the patient is sedated the meticulous and constant care required in noting leaks or obstruction in the airways has to be redoubled.

CASE 6.—E.D., a 47-year-old taxi driver, was admitted to the Queen Mary Veterans' Hospital on March 24, 1961, complaining of increased dyspnea, cough and drowsiness. He had a history of chronic cough dating back to 1942, and had been hospitalized every year since 1957 for exacerbations of chronic bronchitis and emphysema. During an admission in 1958, he was found in a comatose state on one occasion in an oxygen tent and on another occasion after the administration of morphine. In the course of the latter admission, he was found to have exophthalmos, polycythemia and mild diabetes, but endocrine studies were negative.

Physical examination revealed an agitated and confused, obese man, markedly cyanotic and with pronounced exophthalmos and a flapping tremor. He was breathing rapidly and shallowly. Auscultation of his chest revealed bilateral basal inspiratory rales and diffuse, though not prominent, expiratory rhonchi. Some jugular venous distension was noted, but there were no other signs of heart failure. Hiccoughing was present. His rectal temperature was 101.2° F. His hemoglobin value was 20 g. % and hematocrit 68%. A portable chest radiograph revealed enlargement of the heart to the right, large bullae in the right apex, and fibrosis with pleural thickening in the right mid lung field. Some pulmonary congestion was also present. An ECG showed right-axis deviation with p-pulmonale. The arterial pCO_2 value at 1.30 p.m. was 85 mm. Hg; pH 7.28, and bicarbonate 35 mM./l.

arterial pCO_2 had not decreased significantly since the previous determination (see Fig. 6). Hiccoughing and some nausea and vomiting over the next several days proved to be difficult to control; intramuscular diphenhydramine was tried but was discontinued when drowsiness occurred. Another feature was a pocket of air opposite the superior mediastinum on the right side in chest roentgenograms subsequent to tracheotomy which suggested a pneumothorax but which, however, gradually became smaller. This might have been due to the tracheotomy. Melena also occurred, the cause of which has not as yet been determined.

His arterial pCO_2 levels showed a gradual drop towards normal and by March 30, 1961, he was symptom-free; gradual discontinuation of the respirator had been started.

TABLE I.

Case and patient	*Age*	*Sex*	*Diagnosis*	*Precipitating factors*	*Degree[1] of coma*	*Initial* pCO_2	*Initial pH*	*Chief form of therapy*	*Complications*	*Outcome*
1. A.G.M.	50	M	Chronic bronchitis and emphysema	Sedation and resp. infection	4+	122	7.08	Tracheostomy, mech. ventil., vanillic diethylamide	None	Recovery
2. D.B.J.	68	M	Chronic bronchitis and emphysema, bronchiectasis	Resp. infection; cong. ht. failure; sedation?	2+	61	7.34	Bronchodilators, antibiotics, vanillic diethylamide, diuretics	Electrolyte imbalance	Transient improvement
3. J.A.R.	63	M	Chronic bronchitis and emphysema	Cong. ht. failure; sedation?	4+	66[2]	7.20	Tracheostomy,* mech. ventil.	None	Recovery
4. J.L.L.	71	M	Emphysema	Resp. infection	2+	70	7.38	Tracheostomy, mech. ventil., vanillic diethylamide	Shock, status epilepticus	Death
5. A.G.	64	M	Chronic bronchitis and emphysema	Resp. infection, cong. ht. failure	2+	79	7.34	Tracheostomy,* mech. ventil.	None	Recovery
6. E.D.	47	M	Chronic bronchitis and emphysema, pulmonary fibrosis	Resp. infection, cong. ht. failure	2+	85	7.28	Tracheostomy, mech. ventil., vanillic diethylamide	Melena, pneumothorax	Recovery

[1]Degrees of coma: 0; + = dullness, mild drowsiness; 2 + = marked drowsiness, confusion; 3 + = stupor; 4 + = coma.

[2]After partial arousal from coma with therapy.

*Vanillic diethylamide was also used in these two patients (see charts) but was not considered one of the chief forms of therapy as the dosage used was small.

Initial therapy included phlebotomy with removal of 500 c.c. of blood and an intravenous infusion containing 7½ grains of aminophylline and 1000 mg. of vanillic diethylamide run in at 20 drops per minute. A mercurial diuretic was also given, and antibiotics were started. Respirator therapy with a mask was attempted, but the patient resisted this. At 3:30 p.m. he appeared less cyanotic and agitated and the arterial pCO_2 was found to have dropped to 64 mm. Hg, with a rise in pH to 7.38. A tracheotomy was performed at this stage; mechanical assistance to ventilation by the Bird respirator and suctioning of tracheobronchial secretions were initiated.

Postoperatively, to control intractable coughing, the patient was given 75 mg. of meperidine intramuscularly, with the result that he became unresponsive and developed shallow respirations (despite the automatic operation of the Bird respirator). Increasing the rate of the vanillic diethylamide infusion aroused him fairly quickly, after which a good deal of agitation was noted for a short period.

By the second day of treatment the patient was quite clear mentally, and an obvious decrease in the degree of exophthalmos was noted, though the level of

Comment.—Again, the role of infection and sedation in initiating CO_2 narcosis is noted. Another point worthy of note in this patient was the improvement initially with the use of a respiratory stimulant in addition to the other measures utilized. With an uncooperative patient, however, tracheotomy may become necessary, in spite of this improvement, in order to ventilate the lungs more satisfactorily and to remove tracheobronchial secretions.

The effect of sedation, even with tracheotomy and mechanical ventilation, may still be poor, unless ventilation is watched very carefully and increased either by adjusting or changing the type of apparatus used or, as was done in this case, by increasing the dose of respiratory stimulant.

It should also be noted that mechanical respirators may occasionally cause pneumothorax, a fact which should induce caution in the pressures used in patients with large blebs complicating their emphysema.

DISCUSSION

A summary of the clinical picture of acute respiratory failure, its therapy and the results obtained is given in Table I. As can be seen, five of the six patients survived. In the case of the patient who died, Case 4 (J.L.L.), the brain was unfortunately not examined at autopsy and a cerebrovascular accident cannot be excluded. However, the course of events seems to have been that a moderate degree of respiratory failure was considerably aggravated by recurrent leaking of air around the tracheal cannula (owing to deflation of the rubber cuff) as well as by obstruction of the cannula by the rubber cuff in one instance; and the irreversible terminal situation with status epilepticus and circulatory failure appears to have been due to the resulting hypercapnia and hypoxemia, possibly on the basis of cerebral arteriosclerosis. Hickam and Ross[7] have previously pointed out that difficulties may arise in maintaining a leak-proof airway with positive pressure respiration through a tracheal stoma; the same problem arose in two other patients in this group. Undoubtedly small leaks can be compensated for by increasing the ventilation, but the patients should be observed carefully for the cause of the leak, which should be corrected as speedily as possible.

The question arises as to whether Case 4 could have been managed more successfully without a tracheotomy, as was tried in Case 2. The patient's resistance to the mask made this procedure necessary. Certainly, in mild cases of respiratory acidosis the effects of a conservative therapeutic approach may be determined first, utilizing antibiotics, bronchodilators, continuous mechanical ventilation through a mask or even intermittently at frequent intervals, and respiratory stimulants. Mechanical ventilation through a tracheotomy is a much more reliable method of providing continuing assistance to respiration and is certainly indicated in the more severe degrees of respiratory acidosis, particularly when retained secretions are a factor. Difficulties with the airway must be anticipated and corrected as they arise, by a well-trained team of observers. The establishment of ventilation through a tracheotomy does not permit any relaxation of attention to these patients, even if a respirator delivering a constant minute volume is used. The administration of sedatives is necessary only in exceptional circumstances, since they eliminate an important guide in following the course of the illness, that is, the patient's state of consciousness.

With regard to the use of vanillic diethylamide for such patients, the capacity to produce hyperventilation with the intravenous form is suggested by the prompt lowering of arterial pCO_2 achieved without the concomitant use of a respirator at the start of treatment in Cases 4 and 6 and in Case 2 where the intermittent use of the Bird machine seemed by itself to have been ineffective. The agent may conceivably have played some part in improving ventilation in Case 1, but any such effect was obscured by the use of other modes of therapy at the same time. It did, however, rouse the patient very promptly to a state of consciousness. It is evident that its effect is not limited to the respiratory centre, and it has the capacity to induce convulsions and agitation, necessitating caution in dosage, particularly in patients with only mild degrees of central nervous system depression. The most satisfactory method of administration seems to have been as a continuous intravenous infusion varying in concentration from 1000 mg. in 200 c.c. to 500 mg. in 500 c.c. of fluid, infused at a rate between 20 and 40 drops per minute, depending, as has already been indicated, on the severity of the disturbance. Further experience with the agent appears necessary, but present experience suggests that it may prove to be a useful adjunctive mode of therapy in the treatment of acute respiratory failure in emphysema, particularly in the milder cases where the need for tracheotomy might thereby be obviated.

SUMMARY

Case reports have been presented of episodes of acute respiratory failure in six patients with emphysema. After treatment with a regimen which included tracheotomy with frequent aspiration of secretions, mechanical assistance to ventilation, bronchodilators, antibiotics and a recently introduced respiratory stimulant, vanillic diethylamide, one patient died and five patients recovered. Of the survivors, one showed only a transient period of improvement. Clinical and biochemical improvement was observed in some of the patients with the use of intravenous vanillic diethylamide. This drug may prove to be a useful adjunct to therapy in acute respiratory acidosis and perhaps an alternative to tracheotomy in the milder forms of this disorder.

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REFERENCES

1. SAID, S. I.: *Fed. Proc.*, 19: 373, 1960.
2. COLE, G. W., MARKS, A. AND BAUM, G. L.: *J. A. M. A.*, 174: 896, 1960.
3. BERNSTINE, M. L. AND MOSKAL, J. P.: *Anesthesiology*, 21: 90, 1960 (abstract).
4. DAVIDSON, L. A. G.: *Lancet*, 1: 597, 1959.
5. MUNCK, O., KRISTENSEN, H. S. AND LASSEN, H. C. A.: *Ibid.*, 1: 66, 1961.
6. DORNHORST, A. C.: *Ibid.*, 1: 1185, 1955.
7. HICKAM, J. B. AND ROSS, J. C.: *Progr. Cardiov. Dis.*, 1: 309, 1958.

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SPECIAL ARTICLE

HIGH-VACUUM STERILIZERS* A NOTE FOR SURGEONS AND OTHERS CONSIDERING NEW STERILIZING EQUIPMENT FOR HOSPITALS

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IN THE LAST two years articles in scientific and professional journals and visits from manufacturers' representatives have brought to the attention of surgeons and hospitals a new type of steam sterilizer, often referred to as a "high-vacuum steam sterilizer". The advantages of this type of machine and explanation of the principles involved have been discussed.[1-3] No specifications for the guidance of manufacturers have yet been officially adopted in Canada or the U.S.A., but those set out by the British Standards Institute following the reports of the Medical Research Council's working party on steam sterilization are being accepted as a guide.

It has not been easy to translate the recommendations of the British workers into economic commercial propositions, and therefore a potential customer should be aware of the essential features necessary in high-vacuum steam sterilizing equipment. New equipment is both complex and expensive and cannot be regarded in quite the same light as the more familiar gravity displacement machines in common use. In the new machines the steam chamber is the simplest part of the design, whereas the ancillary electronics and auxiliary equipment decide the quality and performance of the machine.

The principle of operation is that air is withdrawn from the chamber by a pump until the absolute pressure is less than 20 mm. Hg. Steam is admitted at a temperature and for a time necessary to kill all organisms and spores of medical importance. At the end of the sterilizing cycle steam is pumped out and sterile air is admitted to the chamber until atmospheric pressure is reached. Total cycle time depends on the temperature at which the machine is set, but it can be as low as 15 minutes. A good high-vacuum steam sterilizer can handle in a given time approximately four times the load of a gravity displacement machine. Furthermore, sterilization is more predictable, and fabrics and gloves will last longer, owing to less oxidation and heat exposure.

The success of such machines depends on a number of critical factors:

1. *Initial vacuum.*—The initial vacuum must be such that the absolute pressure in the chamber can be reduced below 20 mm. Hg before admission of steam. Knox[4] established this figure experimentally and showed that predictable results depended upon it. It has since been confirmed by others, and there is no reason to believe that a lesser degree of vacuum can be accepted. It is important, therefore, to use a machine which can achieve this vacuum within a short period (say, three or four minutes) and that the reserve of the pump is such that it is likely to be able to reach such a vacuum repeatedly during the life of the machine. As this initial vacuum is so critical, and the whole principle of operation of high-vacuum sterilizing depends upon it, visual indication in the form of a gauge which can measure absolute pressure is essential.

2. *Automatic control.*—Since the whole operation of a high-vacuum machine from the start to the finish of sterilizing a load may be as short as 15 minutes, it is clearly impossible for such a machine to be operated in its various cycles manually. For this reason, manufacturers have made such machines automatic. However, there are several points in connection with automatic control which need to be considered, and it is certainly true that in some cases commercial products fall short in this respect. First of all, a high-vacuum machine may have been installed instead of two or three gravity-displacement-type machines. If a defect occurs in the electrical circuit or any part of the automatic cycling, the sole machine in a hospital could become completely inoperative unless alternative manual operation as a gravity-displacement machine was possible. It is essential that such alternative control be available, although it should not normally be accessible when the machine is under electronic control. A selector handle could normally be locked until a responsible person had decided it was necessary to use it. Most modern machines which are fitted with automatic timing, whether they be of the high-vacuum or gravity-displacement type, depend on a temperature-sensing element in the chamber discharge line linked electrically with a timing device. Such timing does not commence until a certain temperature is reached in the discharge line. Thus, a temperature in a discharge line of only a degree or two below the desired temperature could exist for a long time while the load is being exposed to a high temperature without any of this exposure being counted towards sterilizing time. Some manufacturers have approached this problem by including an integrating temperature-timing device, and others by causing the whole cycle to be stopped and to re-commence if the appropriate temperature is not reached within a reasonable period of time. One or other method certainly should be incorporated, and probably the first method is the better.

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Unfortunately (and unnecessarily) it seems to have become the practice to adopt a sterilizing pressure of 30 or 32 lb. per square inch (p.s.i.), at which pressure saturated steam will kill all organisms of medical importance in two or three minutes. With this short sterilizing time a 50% safety margin is in theory only one minute, but in practice the quality of electronic controls and the various sensing elements may not be such that one can accept such a short additional time for safety. If one adds many more minutes to take care of possible crudeness in control, the advantages of the high-pressure temperature are more than counteracted by the decrease in the life of fabrics. It is the author's opinion that the saving of a few minutes by using high pressures is not justified, and that pressures of 20 or 25 p.s.i. are perfectly adequate and much more easy to control automatically. This being so, it should be possible for the customer to select his operating pressure, although this selection should not be accessible to the operator.

3. *Sensing elements.*—For reasons stated earlier, it is very important that steam should not be admitted to the chamber until the desired degree of vacuum has been reached. It follows that the logical method of ensuring that this does not occur is to incorporate a vacuum switch, compensated for atmospheric pressure, to operate the change from the vacuum cycle to the sterilizing cycle. It is not considered satisfactory to rely merely on a certain time cycle for the pump because for various reasons the pump may not be performing properly, or an exceptional load may demand unusual pumping.

The temperature-sensing element must be placed in such a position (usually in the discharge line) that it is likely to register temperature within a degree or so of that occurring in the centre of the coolest pack. It is possible for the sensing thermometer to be influenced unduly by the temperature of the jacket shell or to be unduly cooled by air-flow around the discharge line. Whether or not the temperature element is functioning satisfactorily can only be judged by performing a test of the machine *in situ*, and this should always be done before final acceptance.

4. *Vacuum breaking.*—At the end of the period of final vacuum which has removed the steam, air must be admitted to the chamber, and of course this air must be sterile or else the sterilized contents of the chamber will be contaminated. Most manufacturers have incorporated a satisfactory filter through which the air is admitted, but the life of these filters is not indefinite, and bacteriological tests should be carried out at installation and periodically afterwards to ensure that no contaminated air can enter the chamber. In this connection it must be remembered that any leaks in the piping connected to the chamber or in the door seal may permit unsterile air to enter the chamber while this is under vacuum. For this reason it is extremely important that engineers who carry out maintenance or inspection of the machines appreciate that joints must be vacuum-tight and that the use of a soft solder and steam-fitting methods are not always satisfactory.

5. *Gauges and charts.*—It can be argued that since in the majority of hospitals no qualified person ever looks at the temperature charts, there is no point in providing an efficient record of a machine's performance. On some machines the chart is so small that it is impossible to interpret accurately the behaviour of the machine during a cycle as short as 15 or 20 minutes. The customer should decide whether or not he wishes to maintain such a record and, if he does, this clearly must be large enough for accurate reading. In the author's view, these machines are still in such an early stage of development that qualified inspection of their behaviour is necessary; therefore adequate charts and gauges should be provided. The need for a suitable absolute pressure gauge has already been mentioned, and a strong case can be made for the fitting of accurate large pressure gauges. A record of temperature alone is meaningful only if one can rely absolutely on the pressure of the steam being fed to the chamber. Certainly with modern devices and reducing valves, the pressure usually is not liable to significant fluctuations. However, the writer would prefer to see a record made by a two-pen recorder, one recording pressure and the other temperature, so as to allow a proper comparison between temperature and pressure to ensure that superheating is not occurring.

6. *Pumps.*—Machines may employ one pump capable of removing air in the initial cycle and steam in the final vacuum cycle, or two separate pumps may be employed. It is not difficult to provide a pump which will remove steam and lower pressure in the chamber to around 50 mm. Hg (absolute), but the requirement of 20 mm. Hg (absolute) in the initial stage is close to the limit of performance of certain very reliable and economical pumps. These features are highly desirable in a manufactured item and are thus attractive to manufacturers. Pumps which can reach 20 mm. Hg and below, with a satisfactory degree of reserve, are more expensive and more complicated, but these can be obtained on some sterilizers offered. It is necessary for the customer to be sure that the pump fitted is likely to be able to achieve the desired degree of vacuum, not only within a few months of purchase, but throughout the expected life of the machine.

TESTING STERILIZERS

In the last three or four years the author has had the opportunity of testing a number of prototype and production vacuum sterilizers. Some of the methods which have been used to test these machines would not be carried out by the average hospital, but certain tests are relatively simple and should be made conditions of accepting new machines. In addition to operating the machine according to the manufacturers' instructions and

including spore strips and temperature monitors in the usual way, the following tests are considered desirable.

1. *Temperature-time tests.*—Two or three thermocouples and a manual recording potentiometer need to be employed, and these items are not too difficult to obtain. One thermocouple should be attached to the side of the discharge line thermometer and the other left free in the chamber. With the chamber empty, temperatures should be recorded by both thermocouples with steam under pressure in the chamber, and the experiment should be repeated with thermocouples reversed. The difference between the temperatures recorded at the two sites should not be greater than 1° C. With one thermocouple placed in the centre of an average-sized pack so that no channel for steam can pass along the path of the thermocouple, and the other thermocouple free in the chamber, a series of readings by both thermocouples should be recorded throughout the whole cycle of operation of the machine. The pack is best placed, alone in the chamber, in the lower front position. While these readings are being made, careful note should be taken of the precise moment when the sterilization cycle starts timing (indicated usually by a light), and readings should be taken of the pen recorder or gauge indication of the temperature. This experiment should be repeated on a number of occasions, and particular attention paid to any discrepancy between the chamber temperature and that of the centre of the pack at the moment when sterilization is indicated as starting. Any discrepancy between the temperature gauges or pen recorders and the temperature in the chamber should also be noted. The same experiment can be conducted with more thermocouples in different packs in the chamber. The author has found that the simplest and most testing conditions occur when a single pack is placed in the lower front of the chamber. On most of the early machines tested, the temperature in the centre of the pack at the moment when the machine indicated that sterilization had started was well below sterilizing temperature. In two cases this temperature remained below that which could be considered sterilizing until the machine itself had indicated that sterilizing was complete—which shows how vital it is to make such tests. No amount of stainless steel, pretty lights or glib salesmanship can deny evidence of this kind. It is true to say that machines which have been inspected recently have not shown this fault, but it did happen last year on a new machine installed in one hospital.

2. *Air filter and leaks.*—The services of a bacteriologist should be employed to check the filters. This is very easily done by finding the orifice through which air is admitted to the chamber, and placing sampling material here which can be cultured. An engineer should be asked to make careful inspection of all piping and door-seals while the chamber is under vacuum, and the machine should not be accepted if any such leaks occur, even though the pump has sufficient capacity to overcome them, because contaminated air could be admitted through these leaks in the post-sterilization cycle.

3. *Vacuum.*—The actual pressure within the chamber during the vacuum cycles should be measured by a manometer. This can easily be done by having a nipple fitted into the back of the chamber. Pressure against time should be plotted on a graph, and particular attention paid to the way in which the curve flattens out. If the pump is only capable of reaching a few millimetres below 20 mm. Hg (absolute) when it is new, it is unlikely that it will continue to achieve the desired figure as it gets older.

It may seem that it is unreasonable to expect a hospital to carry out these tests before it accepts a new sterilizer; this of course is a decision which hospitals must make for themselves. If the surgeons of the hospital, and others concerned, expect items marked "sterile" to mean that they can be guaranteed free of organisms and spores of medical importance, then it is necessary for someone to carry out this type of inspection before acceptance, and for some modified periodic inspection to be carried out during the life of the machine. Neither spore-strips nor temperature indicators can give a complete guarantee that a machine is operating properly. This can only be achieved by intelligent inspection of gauges and pen recordings, periodic checks with thermocouples, and by adopting some technique for bacteriological tests such as that suggested by Howie.[5]

SUMMARY

High-vacuum steam sterilizers are very different in design from sterilizers at present in use in most hospitals. Not all of the difficulties of design and manufacture have been overcome. Therefore, hospitals and, in particular, surgeons should be aware of possible shortcomings.

Before the installation of a machine is contracted for, the specifications should be critically examined, especially in regard to the capacity and reserve of the vacuum pump, adequacy of the recorder and gauges, versatility of temperature setting and flexibility of control. After installation, careful inspection should be made of temperature and other sensing elements, and of the chamber door and piping for leaks under vacuum, as well as a thorough bacteriological and temperature testing of loads under working conditions.

Periodic examinations, both bacteriological and mechanical, are recommended to ensure that initial and final vacua reach required minimal standards; that no superheating occurs; that air admitted to the chamber to break vacuum is sterile; and that spores of medical importance cannot survive anywhere within a load being sterilized.

REFERENCES

1. Great Britain Medical Research Council, Working Party on Pressure Steam Sterilisers: *Lancet*, 1: 425, 1959.
2. WARNER, P.: *Canad. Hosp.*, 38: 33, 1961.
3. KNOX, R. AND PENIKETT, E. J. K.: *Brit. M. J.*, 1: 680, 1958.
4. KNOX, R.: *J. Clin. Path.*, 14: 11, 1961.
5. HOWIE, J. W. AND TIMBURY, M. C.: *Lancet*, 2: 669, 1956.

CASE REPORT

PARADOXIC EMBOLISM DIAGNOSED DURING LIFE, WITH SIGNS SUGGESTING RECANALIZATION OF AN OCCLUDED PULMONARY ARTERY

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ALTHOUGH paradoxic embolism is mentioned in most textbooks of medicine and pathology, the number of cases described in the medical literature remains relatively small. Approximately 100 have been described, and in one-half of these there was a thrombus *in situ* in the foramen ovale.[1] The diagnosis in every instance was made post mortem.

F.V.K., a 39-year-old man, was admitted to the University Hospital on an emergency basis on February 18, 1961. At about 4.30 p.m. on the day of admission, while walking around his house, he experienced the sudden onset of numbness, pain and weakness in his legs ascending from the toes to the hips. In a few minutes he was unable to move his legs and had complete loss of sensation in them. Within 30 minutes, however, he began to recover some sensation and movement in his legs. At the time of examination in hospital some five hours later, his legs were pale and slightly cool, but there was no loss of movement. The femoral pulses were diminished and no pulses could be felt with certainty below the femorals. Sensation to pin prick was diminished, but deep tendon reflexes appeared normal. The patient's physical examination was otherwise unremarkable.

A diagnosis of "saddle" embolism lodged at the bifurcation of the abdominal aorta with fragmentation of the embolus and partial occlusion of both iliacs was made. Upon transfer to the operating room, it was noted that his left foot had become quite pale and cold. The left femoral and dorsalis pedis pulses were absent and the right dorsalis pedis could barely be felt. An embolectomy was performed by Dr. E. M. Nanson. The left common iliac and external iliac arteries were blocked from proximal to the origin of the internal iliac down to the origin of the superficial femoral. An incision was made in the common femoral artery just proximal to the origin of the profunda femoris and a clot four to five inches long was extracted. Following this, good pulses could be felt in the left leg and foot. He was treated with anticoagulants and made steady improvement.

This patient was first seen by the author on March 3, 1961, and a complete history relating to his illness was obtained. He had been in good health until one year before, when he first experienced generalized aching and pain in his right leg while walking, and had to stay home for one week. He thought that his leg was swollen at the time, but crude measurement with a string showed its girth to be the same as that on the left. His present illness began when he attended a convention, during which time he spent the better part of three days sitting in a rather cramped position with his legs crossed. The pain in his right leg recurred and became quite troublesome. During the next few days, he did a good deal of driving and his leg became increasingly painful. Shortly after returning home, which was about one week before his admission on February 18, 1961, he noted the gradual onset of shortness of breath. During the next four or five days, this became progressively worse, so that he could not climb the six steps to his back door without experiencing intense dyspnea. Two days later he experienced the sudden onset of numbness in his legs which resulted in his admission to hospital.

The family history revealed that his father, mother and seven siblings had all suffered with phlebitis and sore and swollen legs. He had been regarded as the fortunate one in the family because of his freedom from venous thrombosis. One brother had an episode of chest pain and hemoptysis one year previously.

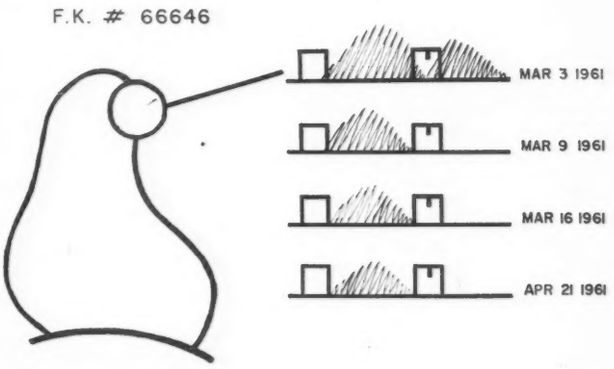

Fig. 1.—Evolution of murmurs heard over main and pulmonary artery listening post. (See text.)

On examination, the salient findings were in the cardiovascular system and right leg. Pulse was 74 per minute, with normal volume and tension. Blood pressure was 115/75. Jugular venous pressure was not increased. The heart was not increased in size but, on listening over the second left interspace parasternally, a definite and sharply localized murmur could be heard extending through systole and diastole (Fig. 1). It could also be heard in a localized area over the left back and in the left axilla. The right calf was tender to palpation, although not grossly swollen. His electrocardiograms were reviewed and were considered to show the evolution of recent pulmonary embolism (Fig. 2). Radiographs of the chest were normal.

My clinical impression was recurrent deep venous thrombosis in the right leg with multiple pulmonary emboli. The episode of systemic "saddle" embolism was thought to be due to paradoxic embolism through a patent foramen ovale or a patent ductus. A venogram was performed in the right leg on March 8, 1961, and despite considerable effort no visualization of the deep veins was apparent. Cardiac catheterization was carried

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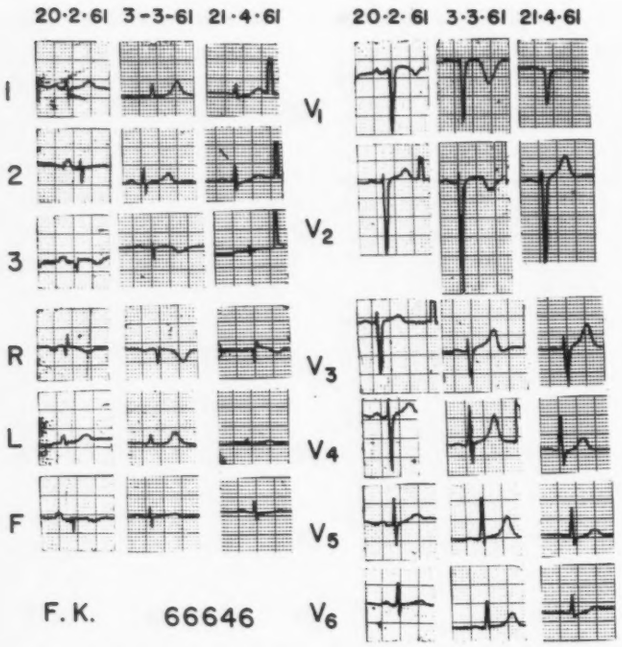

Fig. 2.—Serial electrocardiograms. Note shift in axes of QRS and T, strongly suggestive of acute cor pulmonale (pulmonary embolism). This is best seen in the first and second tracings.

DISCUSSION

In order for paradoxic embolism to occur, the following conditions must be fulfilled: (a) there must be a source of emboli on the venous side of the circulation; (b) there must be a communication between the venous and arterial sides of the circulation, usually a patent foramen ovale; and (c) there must be a reversal of the usual pressure gradient between the right and left atria to permit right-to-left flow through the foramen ovale.

All of these conditions were fulfilled in this patient. From the clinical history, there can be little doubt that he had venous thrombosis in his right leg and suffered pulmonary embolism (single or multiple). The latter event would explain the severe dyspnea which developed during the week prior to the paradoxic embolism. The presence of signs of cor pulmonale on the electrocardiogram would suggest that the pressure in the pulmonary circuit was elevated. The pulmonary artery pressure of 45 mm. Hg which was present some three weeks after the event is still well above normal, 25 mm. Hg. The patency of the foramen ovale was demonstrated on March 12, by Dr. J. E. Merriman (Table I). The pulmonary artery pressure was 45 mm. Hg systolic and there was no evidence of a ductus. Dye curves from the right, left and main pulmonary arteries were normal but those from the right atrium, performed during a Valsalva maneuver, revealed evidence of a right-to-left shunt (Fig. 3). Eventually the catheter was passed across the auricular septum from the right auricle to the left auricle through a patent foramen ovale.

TABLE I.—CARDIAC CATHETERIZATION DATA

	S.V.C.	*I.V.C.*	*R.A.*	*R.V.*	*P.A.*		*L.A.*	*B.A.*
					Main	*Rt.*		
Per cent saturation	62	66	66	61	64	64	98	
Pressures systolic/diastolic (mm. Hg)			11/3	45/0/5	41/14		17/6	129/73
Mean			6.4		25		10.6	92

The murmurs previously heard over the pulmonary artery, left back and left axilla had changed their character during the week following the author's initial examination (Fig. 1). The diastolic component disappeared and only a systolic murmur could now be heard. It became progressively fainter as time went on. However, it was noted that the murmur could be heard best over the trachea and major bronchi and that it radiated well into the left axilla and back in the distribution of the main bronchus to the left lower lobe. Because of the sequence of changes from no murmur to continuous murmur to systolic murmur of diminishing intensity, a diagnosis of recanalization of a major branch of an occluded pulmonary artery was made. Accordingly, on March 14, a selective angiocardiogram was made with a cardiac catheter in the right ventricle. (The pulmonary artery could not be entered.) Owing to technical difficulties, the injection of dye was not satisfactory and the resultant angiocardiographic films left much to be desired by way of detail. No evidence of pulmonary arterial occlusion could be seen. During his stay in hospital, the patient improved remarkably and was finally discharged on continuous anticoagulant therapy.

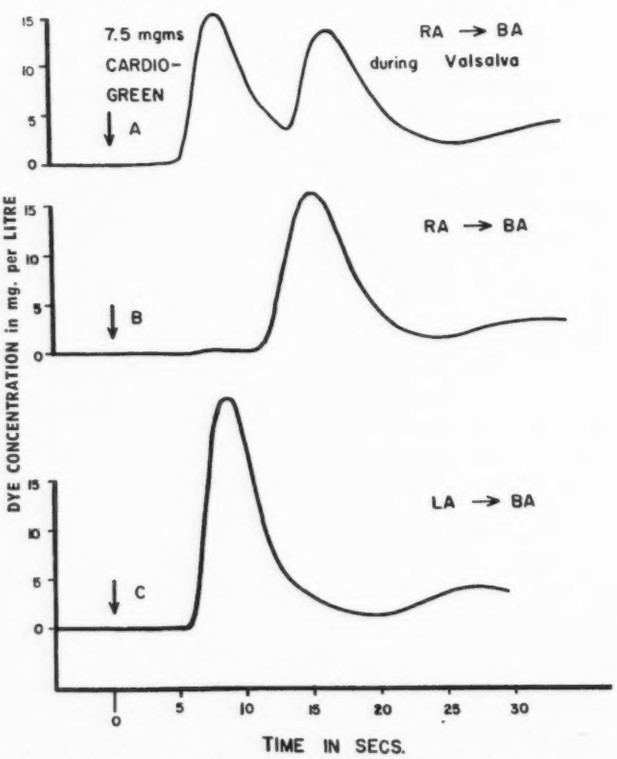

Fig. 3.—Dye dilution curves with recording from brachial artery. Curve C shows the early appearance time expected from an injection into the left auricle. The smooth descending limb of the curve effectively eliminates the possibility of a left-to-right shunt at either the ventricular or aortic levels. Curve B shows a very small, early rise indicating a minimal right-to-left shunt. The remainder of the curve indicates a normal circulatory path. Curve A shows a large hump with early appearance time indicative of a right-to-left shunt of sizable proportions.

strated by passage of a cardiac catheter through it; probably more important was the demonstration of a right-to-left shunt through the patent foramen ovale. Finally, the recovery of a thrombus of a characteristic shape for venous origin from the left iliac artery completes the story. There was nothing to suggest any other site of origin for this thrombus. Our patient was fortunate that the thrombus did not stick in the foramen ovale and occlude it. Elliott and Beamish[2] have shown that when this occurs the "palliative shunt" which permits decompression of the right side of the circulation ceases and death may ensue.

The finding of a "continuous" murmur over the pulmonary artery which underwent a distinctive evolution was of great interest to us. In view of the proven absence of a patent ductus, this murmur most likely arose from a partially occluded pulmonary artery. Its characteristic radiation along the major bronchi of the left lower lobe was due no doubt to its proximity to these structures, resulting in transmitted vibrations in the air column. The disappearance of the diastolic component of this murmur and the gradual diminution of the intensity of the systolic component are compatible with progressive recanalization of an occluded pulmonary artery branch. Murmurs occurring over peripheral sites of stenosis in pulmonary arteries have been described by several authors.[3-6] Eldridge[4] showed that moderate constriction of a pulmonary artery in dogs resulted in a systolic murmur, whereas severe constriction produced a continuous murmur. In the event of complete occlusion of a major branch of a pulmonary artery, no murmur would be heard. However, retraction or recanalization would be expected to produce, firstly, a continuous murmur and then, with further restoration of the lumen, a systolic murmur of lessening intensity; finally, with virtually complete restoration of the lumen, the murmur should disappear completely. Awareness of the significance of the physical signs described should permit the diagnosis of recanalization of a pulmonary artery to be made relatively frequently.

Summary

A case of paradoxic embolism diagnosed during life and confirmed by cardiac catheterization and dye dilution studies is described. Physical signs believed to be due to recanalization of a major branch of the left pulmonary artery were noted and their evolution is described.

References

1. (a) Johnson, B. I.: *J. Clin. Path.*, **4**: 316, 1951.
   (b) Bigelow, N. H.: *Am. J. Med.*, **14**: 648, 1953.
2. Elliott, G. B. and Beamish, R. E.: *Circulation*, **8**: 394, 1953.
3. Arvidsson, H., Karnell, J. and Möller, T.: *Acta radiol.*, **44**: 209, 1955.
4. Eldridge, F., Selzer, A. and Hultgren, H.: *Circulation*, **15**: 865, 1957.
5. Carroll, D.: *Am. J. Med.*, **9**: 175, 1950.
6. Schein, C. J. *et al.*: *A.M.A. Arch. Int. Med.*, **101**: 592, 1958.

SHORT COMMUNICATION

PHOTOGRAPHIC ILLUSTRATION FOR MEDICAL WRITING:* I. INTRODUCTION

DONALD J. CURRIE, M.D. and
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Toronto

The spoken or written word has an established meaning, and the masterful manipulation, choice and arrangement of words will aid the formation of a mental picture. A description by words alone has limitations in conveying an exact meaning.

To understand a picture completely, one must draw on past experience, or depend upon a description. The combination of words and pictures presents a description in the shortest, most simple and accurate manner.

In common with other visual aids, photographs should attract and hold attention. An effective illustration will invite the reader to further study and will help hold his interest. A picture aids memory. A photograph is a permanent record of the appearance of a situation at one time. A photographic copy is an accurate reproduction of an original record and it imparts an impression of authenticity.

Print Quality

Photographs of good quality have certain common features. Details show clearly. Contrast is good, being neither too dark nor too light. Tonal gradation is wide, from black through grey to white. Important areas are not obscured by deep shadows, bright highlights or distracting foreground objects. There is distinct subject-background separation. Where there are series, the photographs should have similar characteristics. Only the area of interest is included. The photograph should be free of finger marks, scratches, dust and dirt marks and emulsion cracks. Prints should be spotted to eliminate minor imperfections. Retouching creates a different and false appearance and should be avoided wherever possible, with the exception of the removal of irrelevant background detail. Quality retouching is expensive and must be done by a competent specialist in this field.

A high-quality halftone illustration requires the use of a fine screen in engraving in order to maintain definition and fine detail. Fine screens are of value only when used with smooth-coated or enamelled paper of uniform surface. A coarse screen is less expensive and is satisfactory with rough paper of newsprint quality. Line illustrations

*From the Departments of Surgery and Photography, St. Michael's Hospital, Toronto.
This is the first of a series of five communications to be published in successive issues.

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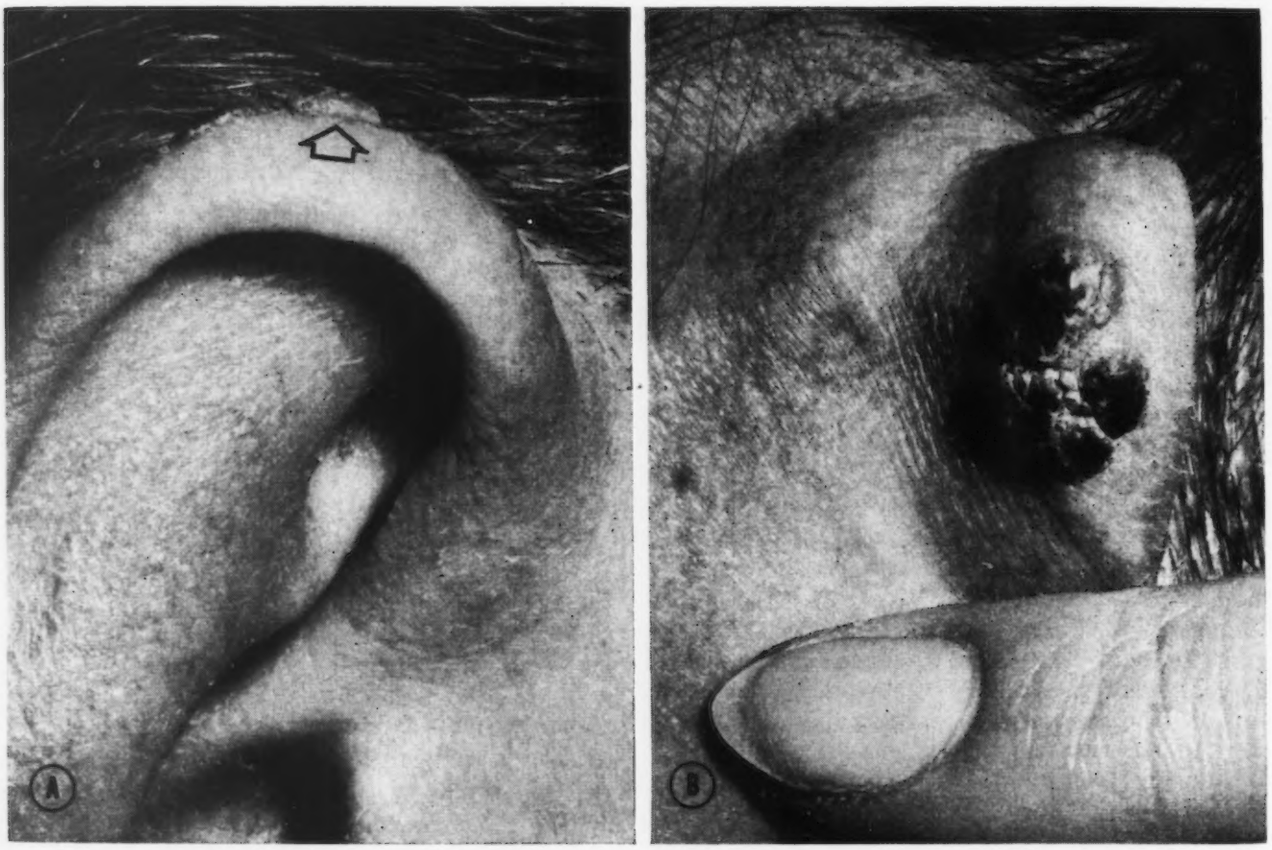

Fig. 1.—A squamous cell carcinoma of the skin on the medial aspect of the right ear. (a) shows the right ear in anatomical position and (b) shows the right ear lobe held forward. An example of a good photograph for publication. It has overall sharpness and good contrast, and the area of interest is well shown. There is good tonal gradation which gives an impression of depth. The photographs match because they have similar characteristics.

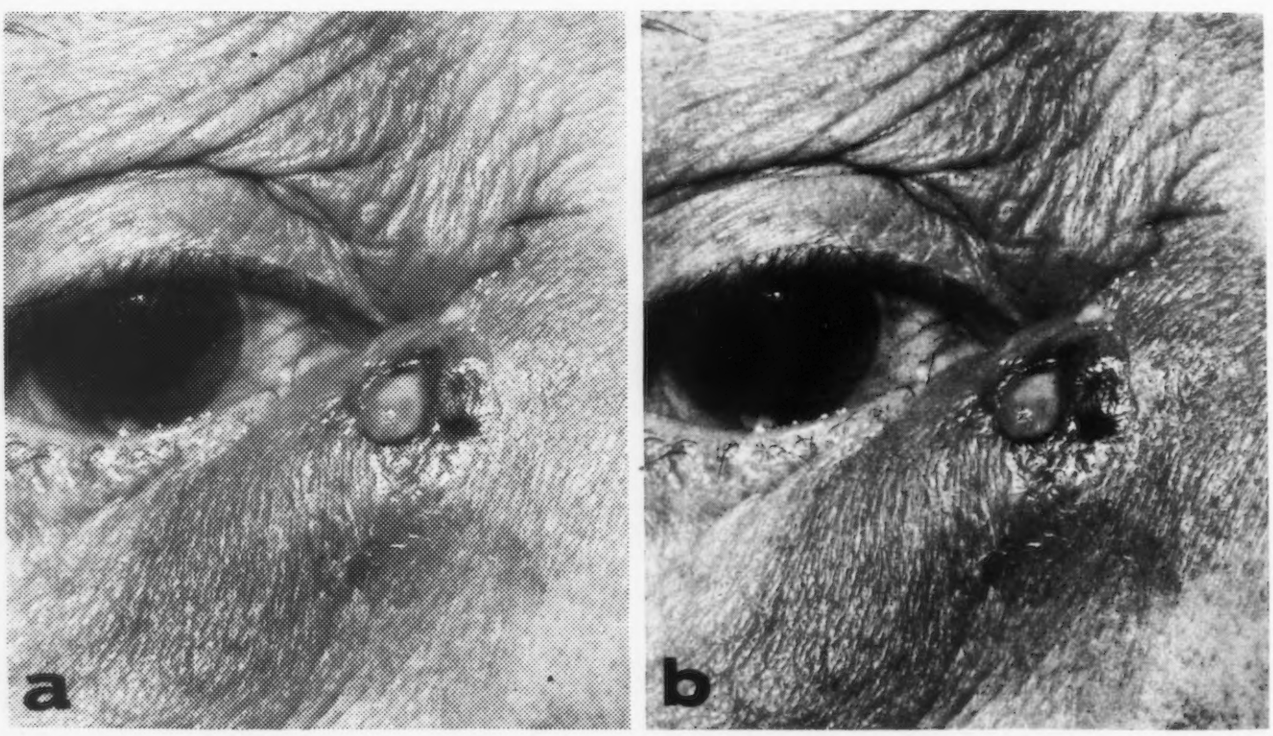

Fig. 2.—Draining sinus due to infection in the right tear sac. The quality of a halftone illustration depends upon the quality of the original photograph, the coarseness of the screen and the finish of the paper. The same original photograph was used for both (a) and (b). A coarse screen of newsprint quality was used in preparing photograph (a) for printing, whereas for (b) a very fine screen was used.

reproduce relatively better on rough-surface paper than do halftone photographs. Lines should be heavier to compensate for roughness of the paper.

Most publishers will prefer ferrotyped glossy prints or smooth-surface white photographic paper. The paper may be single or double weight. The submitted print should not be larger than 11 x 14 inches or smaller than 2 x 3 inches. Each print must be identified on the back by pencil. The top should be indicated. The author's name, the title of the article or book and the figure number are given. The legend is never written on the back of the illustration. All legends are typed separately and submitted with the manuscript. Prints should not be permanently mounted on cardboard stiffeners but they may be lightly tacked at the corners by tape. The face of the print should be protected by plain white paper, and instructions to the engraver may be indicated on this paper. Envelopes should be used for further protection.

COLOUR

Before considering the use of colour illustrations the publisher should be consulted. Illustrations are considerably more expensive to publish in colour than in black and white. Often colour illustrations can only be published at the author's expense. Colour should be used in instances where it has a definite advantage and where subject material cannot be satisfactorily shown in monochrome.

	BLACK & WHITE		LINE BLACK AND			HALFTONE BLACK AND		
PLATE SIZE	line	halftone	1 color	2 colors	3 colors	1 color	2 colors	3 colors
2"X 3"	X	1.5X	2.3X	3X	3.7X	24X	35X	47X
4"X 5"	1.5X	2X	2.7X	4X	5.4X	33X	47X	61X
5"X 7"	1.7X	2.6X	3X	4.5X	6X	38X	56X	70X
6"X 9"	2.3X	3.1X	4X	6X	8X	46X	72X	90X
extra for presswork	44%	44%	57%	72%	86%	57%	72%	86%

Fig. 3.—The cost of making plates for printing. The cost depends on the size of the plate and whether the illustration is line or halftone in black and white or colour. The cost of plate making is roughly estimated in relation to the cost of the least expensive plate. For example, the cost of making a black and three colour halftone plate measuring 2" x 3" is 47 times the cost of making a black and white plate for a line illustration of the same size. To this is added 44% of the cost of the black and white plate and 86% of the cost of the full colour plates for presswork. The relatively high cost of publishing illustrations in colour is shown.

PLANNING PHOTOGRAPHS

As a general rule, the physician is only an occasional author, and it is not expected that he will have experience in all phases of preparing and arranging photographic illustrations for medical writing. He should therefore seek information related to the preparation of photographs from publishers, medical illustrators, pamphlets and books on the subject, and from individuals who have had experience in medical writing. A guide for prospective authors is periodically published in medical journals describing their particular requirements. Book publishers will provide or recommend a prospectus for the guidance of authors.

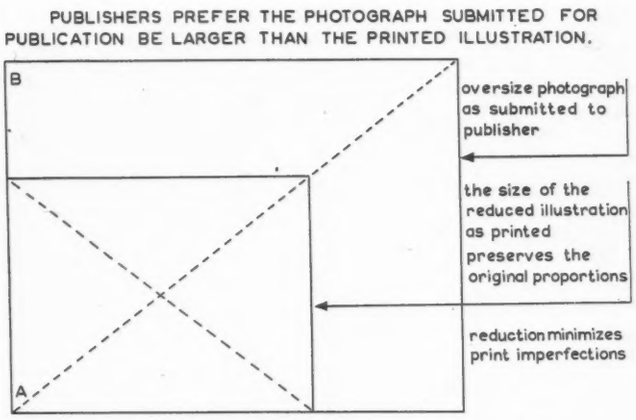

Fig. 4.—Although photographs may be prepared the same size or smaller, photographs which are larger than the intended illustration are the most satisfactory.

Many authors make the mistake of collecting illustrations after the text has been completed. Often these illustrations are not the most suitable, and frequently they are hurriedly and haphazardly included with the manuscript just before submission to the publisher. Illustrations must be planned in detail during the writing of the text. Rough sketches or detailed descriptions of the planned illustrations should be a part of the manuscript during preparation. If possible, the final illustrations should be prepared with the text.

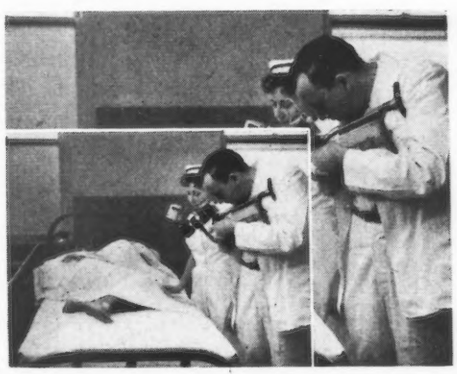

Fig. 5.—The oversized photograph submitted by the author is easily reduced to the required size.

In planning illustrations for medical writing the number and type of illustrations must be considered. It is most important to have reasonable balance between the amount of text and the number of illustrations according to the subject material. The author may be limited by the cost of illustrations. He may have to pay for drawings and photographs, or he may have to hire a medical artist or photographer. The author of an article for a medical journal may be asked by the publisher to reduce the number of illustrations or to pay part of the cost of publication. Illustrations in colour are usually published at the author's expense.

To be able to plan illustrations intelligently it is necessary to know beforehand the dimensions of the page and the number of columns of text to a page. In writing an article for a specific medical

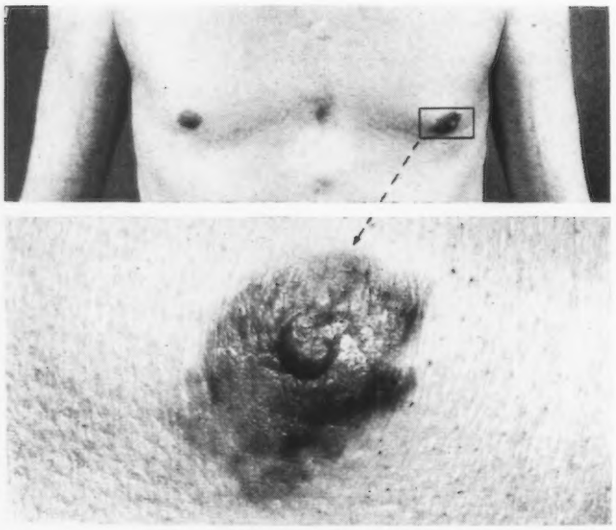

Fig. 6.—In many instances, it is not possible to show an area of interest adequately in one photograph. The general view of the carcinoma in the left breast of a man was supplemented by a close-up to show details. On occasion, several photographs are needed to display the area of interest satisfactorily from several points of view.

journal a back issue will provide a guide for dimensions and arrangement. When planning illustrations, allowance is made for the border and legend. The original print should be 30-50% larger than the final published size. The reduction improves the quality of the published print and an oversized original is preferred by publishers. Same-sized originals or enlargements of originals are possible but undesirable, and some publishers may reject originals of small size.

COLLECTING PHOTOGRAPHS

The author may have illustrations prepared especially for him or he may beg, borrow or steal illustrations from other sources. Some may have illustrations especially prepared by the staff of a hospital department of medical photography. The medical photographer has the widest experience in preparing photographs for medical publication. The author must explain to the medical photographer the purpose and proposed plan and type of illustration if he is to expect the best result. The author will maintain constant supervision during the preparation of photographs and should make every effort to arouse the interest and enthusiasm of the medical photographer and make certain that he receives full credit for his efforts.

Where the services of a medical photographer are not available, the author may have to hire a professional photographer. The services of professional photographers are expensive; they require careful supervision, as they are usually not familiar with medical subjects. The planning of the illustrations will have to be in greater detail, and the author must make certain that the professional photographer fully understands what he wishes to have shown by the photograph. The work of amateur physician-photographers is, as a rule, below the standard of good illustration.

Where a number of original illustrations prepared by pen or brush is required, the medical author should seek the services of one medical artist only, in order to maintain the same style throughout the whole publication.

The medical author will seldom use photographs acquired from other sources, although he may want to use a photograph which was taken originally for another physician. The author of a medical book may use photographs prepared for someone else in quoting an authority, in showing examples of rare conditions or for the sake of economy in using illustrations in colour. Before using published illustrations he must obtain permission in writing from *both the author and the publisher* and must give credit in the legend of the illustration or in the acknowledgments. When an illustration which was prepared for someone else is used, written permission from the owner must be obtained in writing and credit must be given in the publication.

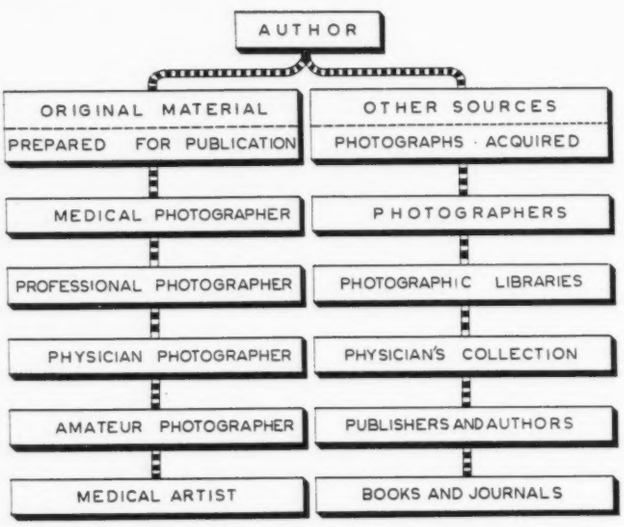

Fig. 7.—Sources of photographs for medical illustration. Photographs may be made especially for the author's publication or they may be begged, borrowed or stolen from other sources.

In borrowing published illustrations the author should always try to obtain the original or a copy of the original photograph. Where available and suitable the original engraving plates may be reused. The author should not have the published halftone illustration copied, as the quality is impaired by the pattern of the screen. As a screen is not used with line illustrations, a published line illustration may be satisfactorily copied for republication.

WORK PLANNING BOARD

Thorough planning of a writing may be facilitated by the use of a work planning board. It will show at a glance the work accomplished, the work ahead and the overall arrangement. The board should be large so that every marker can be easily seen, and it should be flexible so that the markers can be readily interchanged.

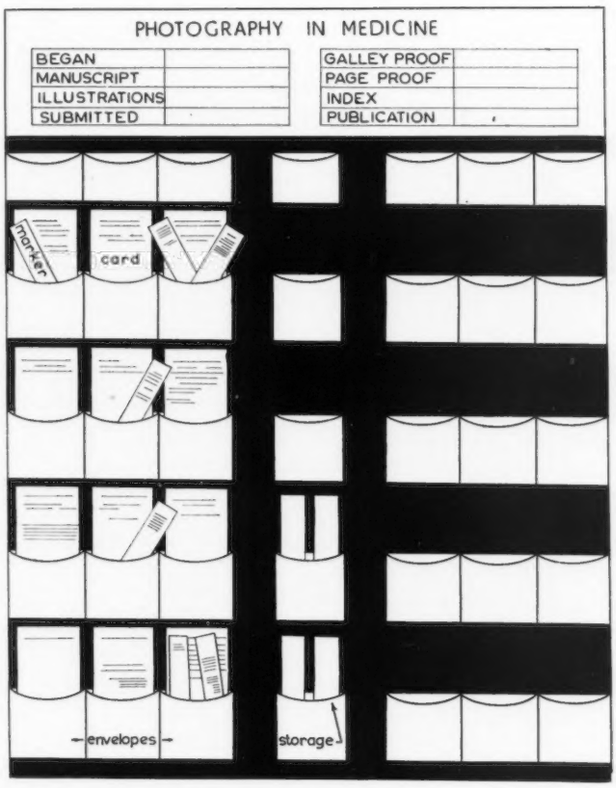

Fig. 8.—The work planning board used in writing "Photography in Medicine". It was found to be of great value in planning and arranging the text and illustrations for this book. The original wall board was 3 x 4 feet.

A work planning board may take many forms. A satisfactory board can be made from a 3 x 4 foot panel of hard cardboard to which is attached a number of open 4 x 5 inch envelopes. Important information is recorded on cards which are inserted in the envelopes. Coloured strips of paper or cardboard are used to show the progress of work. Green markers could be used to indicate the completion of text and red cards might show the completion and number of illustrations for the section of the writing represented by the envelope. The board is posted on a wall in the author's place of work. The use of a work planning board is particularly important where the writing is lengthy and where the material requires good organization. It should encourage the simultaneous preparation of text and illustrations.

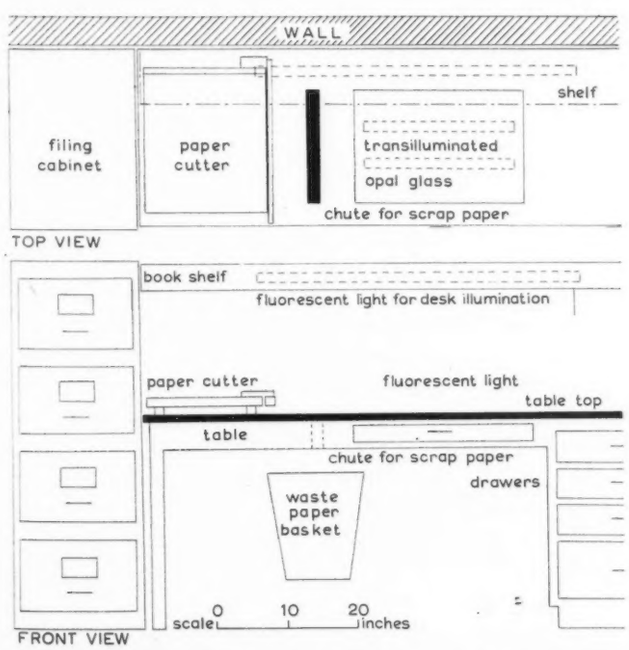

Fig. 9.—A convenient work desk for an author has many features which simplify writing, arranging and editing material for publication.

THE AUTHOR'S DEN

The serious writer should have a place of work which is convenient and which has all of the essential facilities well arranged. A teaching hospital ought to provide space and equipment for serious writing by members of its staff. Similar equipment may be used in the physician's office or in his home. The author's den should be quiet, comfortable and convenient.

It is essential to have a large table-top area so that a number of references, illustrations and notes can be quickly reviewed. An author will need adequate storage space in the form of filing drawers, bookshelves and cupboards. Good general room lighting should be supplemented by additional illumination for the work table.

A transilluminated screen may be built into the table top or may be available as an accessory box for transparencies or radiographs. There should be an adequate supply of writing materials, a telephone and several baskets for waste paper. A dictating machine, drawing board and art supplies, slide viewer and paper trimmer are also needed. The provision of good writing facilities promotes good writing.

The complexities of medical writing today demand adequate and readily available facilities which will encourage medical writers to thoroughly prepare well-illustrated material for publication.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

There is a general misconception of the relation of the intestines to the fluid in the abdomen. The intestines are usually regarded as floating on the surface of the fluid as they would be if in an open vessel and thus not subject to pressure on the free surface. But in the abdomen they are not subject to the pressure of the anterior, abdominal wall, so that the intestines are forced down into the fluid as it rises in the peritoneal cavity, the degree of submerging becoming greater as the quantity of fluid increases and rises in the abdominal cavity. The greater the contents of the intestine, liquid and gaseous, the greater their volume, and the more will they be submerged. It is further to be remembered that at the sides of the abdominal cavity lie the ascending and descending colon, and that they are loosely attached to the posterior part of the outer, abdominal wall, so that, if filled with gas, they float up into the fluid, if not, they lie on the posterior wall.—Alexander McPhedran, *Canad. M. A. J.*, 1: 937, 1911.

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RECENT STUDIES ON RHEUMATIC FEVER, ITS TREATMENT AND PROPHYLAXIS

DESPITE the fact that salicylates have been widely used for many years in the treatment of rheumatic fever, and corticosteroids have been employed for this purpose for over a decade, there is no clear concept of the degree of protection, if any, that either of these therapeutic agents provides against clinically significant rheumatic cardiac sequelae. A number of intriguing and thought-provoking observations concerning this still beclouded area of medicine have emerged from the recently reported studies of Professor Bywaters and his co-workers at the Rheumatism Research Unit of the Canadian Red Cross Memorial Hospital in Taplow, England.[1, 2] The purpose of their investigations was to elucidate the natural course of rheumatic fever treated by no measures other than bed rest, to correlate the degree of rheumatic activity with cardiac damage, to compare results of treatment by bed rest, salicylates and corticosteroids, and to assess the role of each of these therapeutic measures in the management of this disease.

In general, prolonged elevation of temperature and sedimentation rate were more closely related to carditis than was the sleeping pulse rate, although in severe attacks persistent tachycardia was a constant feature and was associated with a poor prognosis. Anemia and weight loss were uncommon and were observed in only the most severely ill patients. Nodules were rarely noted in the absence of carditis but were present in one-quarter of patients with slight heart involvement and in half of those with severe carditis.

The in-hospital course of a group of patients treated by bed rest only was compared with that of a comparable group treated with a six-week course of aspirin, corticosteroids or ACTH, together with prophylactic sulfonamides. Arthritis, fever and sedimentation rates subsided more slowly in the group treated by bed rest alone, but temperatures were comparable in the two groups of patients by the fourth week of the illness, arthritis by the sixth week, and sedimentation rates by the eighth week. Nevertheless, some patients treated by bed rest alone showed a strikingly rapid subsidence of rheumatic activity. There was little difference in changes in cardiac status between the two groups during the six-week period of treatment in hospital.

A third group of patients treated by 12-week courses of either corticosteroids or salicylates fared no better than did those who received corticosteroids, ACTH or salicylates for six weeks only.

As a result of the observations arising from this study these workers postulate that: (1) The majority of cases of rheumatic fever encountered today are mild, and respond satisfactorily to bed rest only. (2) While salicylates are helpful in controlling fever and relieving joint pain and other symptoms, they do not significantly alter the course of the disease or the cardiac status. (3) Although corticosteroids or ACTH may shorten the duration of rheumatic activity, there is no evidence that they have any beneficial effect on rheumatic cardiac lesions except for a possible favourable effect on soft diastolic murmurs while the patient remains in hospital. (4) The delta-steroids (corticosteroids with minimal sodium-retaining effects) are indicated for all patients with cardiac enlargement and marked rheumatic activity, since by suppressing the disease activity, they lessen the likelihood that congestive failure may develop or if heart failure is present they may enhance the therapeutic response to digitalis and diuretics. In such cases salicylates do not adequately control the activity of the disease and are potentially dangerous since they may precipitate pulmonary edema or rheumatic pneumonia.

The latter observation by the Taplow investigators may raise the eyebrows of some workers in other centres who have reported well-documented and well-illustrated instances in which gross cardiac enlargement, pulmonary edema and heart failure subsided just as dramatically in patients treated with salicylates as in similar cases treated with corticosteroids.

In a separately reported study,[2] 198 patients were subjected to follow-up investigation for periods of five to ten years to ascertain the changes in their cardiac status, to evaluate the relation of such changes to rheumatic fever recurrences, and to assess the extent to which cardiac changes were affected by sulfonamide prophylaxis or by treatment with corticosteroids or salicylates. One hundred and twenty-five of these patients had been treated by bed rest only during their initial attack of rheumatic fever, and had received no prophylactic medication. Of these, 19 experienced subse-

quent rheumatic fever recurrences and 106 had no recurrence. Those patients who had no abnormal cardiac manifestations during their initial attack, and who remained free from recurrences, were normal at follow-up examination. Those who had soft (grade 1 or 2) diastolic murmurs during their initial illness were normal at follow-up, or still had soft murmurs, but none were worse. Patients who had more severe carditis, with grade 3 murmurs, during their initial rheumatic attack usually showed no significant change at follow-up examination; in a few of these the physical signs were less pronounced, some even disappearing entirely; in others the abnormal signs became more pronounced (e.g. aortic incompetence increased or opening snaps developed in addition to previously noted mitral systolic murmurs). Among those who developed rheumatic recurrences, however, deterioration was encountered more commonly and some of these patients died. This more serious type of outcome was observed especially in those who were experiencing their second rheumatic attack at the time of their initial admission, or in those who had more than one subsequent recurrence.

With regard to the relationship between cardiac status and total number of attacks of rheumatic fever or chorea, it was noted that at the time of initial admission most patients having their first attack had slight or no carditis while most of those in their second or later attacks had pronounced heart disease. At the final follow-up examination it was noted that the majority of those whose cardiac status had deteriorated (including those who had died) had had three or more rheumatic attacks, and that mitral stenosis developed only in such cases.

Rheumatic recurrences were experienced by 19 of 125 patients (15.2%) who were treated during their rheumatic attacks by bed rest alone, without subsequent prophylactic medication, and by five of 73 patients (6.85%) treated during their rheumatic attacks with six-week courses of ACTH, cortisone or aspirin, and given one gram of sulfonamide daily thereafter on a prophylactic basis.

Amongst those patients who had no recurrences, there was no difference in cardiac status at follow-up examination between those who had been treated by bed rest alone and those who received corticosteroids, ACTH or aspirin, plus sulfonamide prophylaxis. Among those who did experience recurrences, however, there were marked differences in cardiac status between these two treatment groups. Those who received sulfonamide prophylaxis showed less frequent recurrences without cardiac deterioration while those who were given no prophylactic medication experienced greater numbers of recurrences and exhibited more frequent and severe worsening of their cardiac status. These observations led to the conclusion that treatment of acute rheumatic fever in hospital with corticosteroids or salicylates, in most cases, has comparatively little influence on the cardiac status that may be encountered at follow-up examination five to ten years later, but that present-day measures of prophylaxis are beneficial and provide the most effective method currently available for reducing rheumatic fever morbidity and mortality.

REFERENCES

1. BYWATERS, E. G. L. AND THOMAS, G. T.: *Brit. M. J.*, 1: 1628, 1961.
2. THOMAS, G. T.: *Ibid.*, 1: 1635, 1961.

LABORATORY DIAGNOSIS OF VIRUS DISEASES

IN CURRENT practice, the laboratory diagnosis of virus diseases is approached from three fronts: (1) microscopy, (2) virus isolation, and (3) serology.[1] The decision to use any test or set of tests must depend upon the individual case: cytological or histological examination is applicable only when the lesion or eruption is on the surface of the body, or with biopsy or postmortem material; virus culture is the method of preference during the acute phase of an illness when it is now possible to make a provisional diagnosis in a few days by isolation of the causal agent; serological diagnosis, except in specific cases, depends on the comparison of an acute with a convalescent sample of serum, and it is therefore a procedure for retrospective diagnosis. The multiplicity of serological types of many virus groups makes testing for all of them impracticable, and it is therefore usually preferable to concentrate first on virus culture.

The most practical method of culturing viruses is in tissue or cell cultures. Although several such methods are available, each with its own attributes, all are based on the same principle, that tissues removed from an animal host can be cultured in a suitable nutrient medium in glass containers. The advantages of these techniques are many: virtually any animal species within reason can be selected, and virtually any organ can be selected for culture; the cells grown in culture are not affected by the animal's immune mechanisms; cultures can be kept free from bacterial contamination by the use of antibiotics in the medium, while, at the same time, virus growth is unaffected. Two of the more useful culture media currently employed are the trypsinized monolayer cells, and the monolayer with agar overlay. Viruses, being intracellular parasites, are recognized by the effect they produce on the cells in which they multiply. Virus growth in cultures is recognized mainly by the following methods: (a) cytopathic effect, (b) hemagglutination and hemadsorption, and (c) the fluorescent antigen-antibody test.

Despite great advances in tissue and cell culture techniques, the embryonated egg remains a convenient and sensitive medium for isolating a number of viruses, among them, those of influenza, mumps, variola, vaccinia, cowpox, and herpes

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simplex. However, it is the tissue culture methods that have made it possible to carry out neutralization and other serological tests with greater accuracy and on a scale that would have been quite impracticable by any other method.

Serological techniques available include such well-established procedures as the complement-fixation, flocculation, and agglutination tests which have been improved and adapted to virological work, as well as entirely new ones, such as gel-diffusion and fluorescent microscopy techniques.

Neutralizing antibody, which is closely concerned with protection mechanisms, is the most important indication of past infection, is highly specific, and is therefore used for identification of virus strains according to their immunological types. Its presence or absence is of considerable significance in diagnosis and in epidemiological surveys. A neutralization test involves examination of the serum for its capacity to prevent, modify or "neutralize" the effect of a virus by inoculation of serum-virus mixtures into a cell system in which the virus by itself is known to produce an effect. Several alternative methods are available for measuring the antibody titre, which is taken as the highest dilution of serum in which a proportion of the cultures are infected and a proportion protected (50% end-point): (1) the cytopathic method, (2) the metabolic-inhibition or colour test, and (3) the hemadsorption-inhibition test. Antibody to the enteroviruses, poliovirus, the viruses of herpes, measles, and others can be measured by these methods.

Antibody to the myxoviruses (influenza, parainfluenza, mumps, and Newcastle disease) can also be measured by the hemagglutination-inhibition test. Antibody to several of the respiratory viruses (influenza, adenovirus, parainfluenza, and respiratory syncytial viruses) can be detected by the complement-fixation test. The fluorescent antibody technique will measure antibody responses to an agent, such as the Eaton agent isolated from cases of primary atypical pneumonia, which produces little or no effect in inoculated culture.

Serological tests can also be used to determine the presence of viral antigens. The complement-fixation test and the recently described agar-gel precipitation technique will detect viral antigen in tissues in the acute phase of a virus disease such as smallpox. The complement-fixation test can also be used to identify newly isolated strains of influenza virus by means of strain-specific antisera.

In the field of virology, microscopic examination is of value on many occasions. Smears of material taken from the base of cutaneous lesions in the vesicular and early pustular stage of smallpox, vaccinia, varicella-zoster and herpes simplex can be dried and stained with various preparations, to show the general cytological picture (Giemsa), elementary bodies or virus particles (Paschen or Gutstein) and inclusion bodies (hematoxylin and eosin). There is a wet-film method which will show cytological details, but this method is not satisfactory for the study of elementary bodies. Cytology is valuable also in the diagnosis of inclusion conjunctivitis in which intracytoplasmic inclusion bodies can be found in epithelial scrapings, and in the diagnosis of cytomegalic inclusion disease in which epithelial cells with intranuclear inclusions may be found in the urinary sediment.

Microscopic examination of biopsy and post-mortem material likewise helps to establish the diagnosis of many diseases of viral etiology. For example, histological examination in cases of sudden death in children has often led to the diagnosis of poliomyelitis. Negri bodies, well-defined inclusion bodies within the cytoplasm of nerve cells, can be found in a high proportion of dogs infected with rabies. In such circumstances, histological examination provides not only an important diagnostic procedure, but also a guide to the treatment which should be adopted. In the case of both poliomyelitis and rabies, material should be retained for virus isolation, and in the case of rabies, for animal inoculation.

The value and practicability of these laboratory methods for diagnosis of virus diseases are indicated by such striking advances as the isolation and identification of poliomyelitis virus Types 1, 2 and 3, of Coxsackie and ECHO viruses, and of newly recognized respiratory and enteric viruses. Gratifying though such advances may be, the virologist is still confronted by the tantalizing challenges of other virus diseases such as rubella and infectious hepatitis, in which some progress is only now being seen in methods for isolating the causative agent. F.L.

REFERENCE

1. DUDGEON, J. A.: *Brit. M. J.*, 1: 1269, 1961.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

TRANSIENT ATTACKS OF APHASIA AND PARALYSES IN STATES OF HIGH BLOOD PRESSURE AND ARTERIO-SCLEROSIS

Headache, vertigo, convulsions, aphasia, paralyses, and a progressive dementia are among the cerebral manifestations of arterio-sclerosis. Death "at the top" may be slow as in the old oak with which Dean Swift compared himself; or it may be sudden, when a vessel ruptures, or more gradual if thrombosis occurs. These may be called the major manifestations, but there are others less serious, but of great importance as their significance may be overlooked or misinterpreted. To headache and vertigo I will not refer since everyone now recognizes how common they are as early symptoms of arterio-sclerosis in the young, and more constant aphasias and paralyses, cerebral crises as they have been called, occurring in states of high blood pressure and in arterio-sclerosis, to which I wish to call attention. Within a few weeks of each other I have recently seen two cases which illustrate the character of the attacks, and the first case is unusual since so far as could be determined only high blood pressure existed.—Sir William Osler, *Canad. M. A. J.*, 1: 919, 1911.

Letter to the Journal

WHAT IS A PROFESSION?

To the Editor:

The article by Dr. Klass entitled "What is a Profession?" (*Canad. M. A. J.*, 85: 698, 1961) is very interesting and thought-provoking. We all know how the word "profession" has come to include innumerable groups, as the author clearly points out. But do we realize that their legal status is likewise showing subtle changes? The author states that "by statute, a professional group is granted exclusive right of performance in a specific field, be it the practice of law, medicine or engineering". Along with this it has the privilege of setting its own fee structure and the responsibility of disciplining its members and assuring that service is available to all who need it.

In medical matters, however, there is spreading throughout Canada and the United States a tendency to evasion of this "exclusive right". This is done chiefly by practitioners of chiropractic and naturopathy, who claim that their practises are based on a different system of therapy than medicine, and hence that they do not come under the jurisdiction of the Medical Act. They are thus able to set up their own Chiropractic or Naturopathic Act with any standards they desire. In their actual practice they diagnose and treat the same illnesses as do medical doctors: hypertension, strained backs, headaches and so forth.

As for the right to determine our own fee structure, this seems to be diminishing too, with the advent of the large and powerful insurance plans.

So if we are not careful, we may some day be left with all of the responsibilities of a profession but none of its privileges. Would medicine then fade away as a profession?

ARTHUR C. WALSH, M.D.

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Vancouver 6, B.C.

MEDICAL NEWS IN BRIEF

SYRINGE-TRANSMITTED HEPATITIS: A RECENT EPIDEMIC IN HISTORICAL PERSPECTIVE

An epidemic of eight cases of hepatitis in adults has been described recently by Dull (*J. A. M. A.*, 176: 413, 1961) in which transmission of the infection could be attributed most readily to repeated use of inadequately sterilized needles and syringes in a physician's office practice. The patients' exposure and subsequent onset of symptoms were compatible with a "common source" outbreak of serum hepatitis (hepatitis B, homologous serum jaundice).

The review of the evolution of serum hepatitis as a specific syndrome is of great interest, and the examples given of historical and contemporary hepatitis epidemics attributable to a variety of contaminated instruments emphasize the continuing importance of adherence to accepted standards of sterilization. Until reliable *in vitro* methods of determination of minimally effective sterilization are available, it is advised that the sterilization recommendations of the Expert Committee on Hepatitis, World Health Organization, be followed. For instruments and materials which can be subjected to heat, these recommendations include: prompt, thorough washing in water followed either by autoclaving, boiling in water for at least 10 minutes, or baking in dry heat at 180° C. for one hour. Also, it is emphasized that there is considerable evidence demonstrating that the entire syringe-needle unit may become contaminated from a single injection using any route of administration; thus the use of the multiple-dose-syringe technique creates another potential hazard.

A SURVEY OF MELANOMAS

Some interesting observations have recently been reported from Bristol by Petersen, Bodenham and Lloyd (*Proc. Roy. Soc. Med.*, 54: 486, 1961) following a 14-year study of 250 patients with melanomas under their personal care, and the review of an additional 400 consecutive cases registered with the South Western Regional Cancer Bureau. The incidence of melanomas in this region is at least 1.8 per 100,000 and the disease is twice as common in females as in males. The average survival for persons with melanomas is 5%, better than that for all cases of carcinoma of the breast. Melanoma of the leg is particularly common in females under 50 years of age and generally this tumour site is associated with the best prognosis, 75% being free of the disease at five years. Though the foot is much less frequently affected, patients with melanomas at this site have only a 25% chance of surviving for five years. The prognosis is also poor when the trunk is involved, and melanomas at the latter two sites are associated with a high incidence of invaded lymph nodes when first seen.

Two-thirds of the melanomas in the Bristol series arose in pre-existing benign lesions which were nearly always lentigines (a simple type of pigmented nevus); only a few melanomas developed from other types of pigmented nevi. Over one-third were present at birth, and one-third had been present for more than 10 years at the time of this survey. Ulceration at the time of first treatment was associated with a poor prognosis, but those lesions which had not ulcerated did well. Cell type did not affect the prognosis, but when invasion of the dermal lymphatics was seen micro-

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scopically dissemination was likely, though not inevitable.

The results of prophylactic radical lymph node dissection were found to be better if an interval of three weeks was permitted to elapse between excision of the primary tumour and the node clearance. Simultaneous dissection in continuity is the method of choice where the primary tumour and the affected lymph nodes are in reasonable proximity. The results of therapeutic node dissection are poor by comparison. Clinical diagnosis by experienced observers based on a careful history and naked-eye examination is correct in 90% of cases and definitive treatment can then be carried out without delay; if there is any doubt, an excision with a 1 cm. margin is carried out and, if positive, a suitable radical excision is then performed.

Treatment should have one object, to rid the patient of his disease. The extent of the surgery can bear some relation to the degree of malignancy; for example, the superficial facial type of lesion in elderly people does well after excision that extends through a 1 to 2 cm. margin of healthy tissue but in other areas the margin should include up to 5 to 7 cm. of healthy tissue laterally and distally, and up to 10 to 15 cm. proximally, together with the underlying deep fascia.

The defects are covered with split grafts which can readily be obtained in adequate quantity and act as a "window" for observation at follow-up examination. Any recurrence should be treated as a matter of urgency and with the same margins of excision as in the primary operation.

Perfusion with cytotoxic drugs of the nitrogen mustard group has a significant effect on melanomas but unfortunately this effect is only temporary and operation must still remain the treatment of choice in all except the most advanced cases.

Local perfusion can be combined with operation in the treatment of primary melanomas of the foot because these have such a poor prognosis.

The authors of this report observe that about 100 fresh cases of melanoma of the foot can be expected each year in England and Wales, and express the opinion that concentration of these cases in two or three special centres would facilitate more rapid collection of valuable data that could contribute to further improvement in therapeutic results.

STARCH GEL ELECTROPHORESIS IN MULTIPLE MYELOMA

In recent years it has been appreciated that there is both diversity and complexity in the protein alterations in diseases such as multiple myeloma, macroglobulinemia and other forms of dysproteinemia. Experience with a new technique for the study of abnormal proteins in human serum and urine, starch gel electrophoresis, was recently reported by Engle *et al. (J. Lab. & Clin. Med.*, 58: 1, 1961). The results are discussed in 72 patients: 56 with multiple myeloma, three possibly in the early stages of multiple myeloma; five with macroglobulinemia and eight others with abnormal peaks in the electrophoretic patterns only. This method of electrophoresis gives high resolution of protein components; it is capable of separating the proteins of normal human serum into over 20 fractions, and the method allows a more detailed assessment of protein alterations than can be obtained by other methods.

The protein abnormality in multiple myeloma is frequently complex. In the serum patterns usually a single abnormal peak was found, but in eight cases, two were seen; in three cases, three; and in one case, four peaks were seen. Among the urinary Bence-Jones protein patterns, in seven cases, four bands were seen; in 10 cases, three; in 12 cases, two; and in nine cases, one band was seen. There was also some evidence for heterogeneity in the latter nine cases.

In the majority of cases of multiple myeloma each patient is known to produce at least two aberrant proteins, the myeloma protein which appears in the serum and the Bence-Jones protein which is excreted in the urine. They are both believed to be derived from the abnormal plasma cells which are characteristic of the disease. When both proteins are present in the same patient, the mobilities of the two proteins are usually different. The abnormal peaks in the serum and/or urine of an individual patient maintain the same mobility throughout the course of the disease. Usually, a single abnormal protein component is found upon serum electrophoresis in any one patient; in rare instances two or three components have been described. For routine diagnostic purposes, when only one method is used, the starch gel has no great advantage over filter paper. However, as a research tool in the study of multiple myeloma and related diseases, the starch gel method has some important advantages.

PERIODIC DISEASE

For the last 20 years there have been reports in the literature on a peculiar disease which has been known as paroxysmal benign peritonitis, familial recurrent peritonitis, paroxysmal syndrome, periodic disease, etc. Two recent reports draw attention to this peculiar disease. Stoyanov and Schopov (*Klinicheskaia Meditsina*, 39: 141, 1961) describe four cases in patients aged 10, 22, 42 and 36 years, respectively. The main features of the disease were recurrent attacks of fever, abdominal pain with or without ascites and general malaise. In some of the patients attacks occurred every six months; in others, every year. Although the attacks, which last several weeks to two months, can be very severe, no permanent damage to the cardiovascular or any other systems has been noted after many years of recurrences.

Tikhomirov (in the same issue) also draws attention to this disease, which he observed in four patients. It is of interest that one patient's uncle was known to have similar attacks. Since acute, severe abdominal pain with peritoneal irritation plus chills and leukocytosis are a frequent feature of this disease, it is important to keep periodic disease in mind in order to avoid needless operations. Tikhomirov distinguishes two main forms—the abdominal syndrome (with generalized chest pain and difficulty in breathing) and an arthralgic syndrome with marked myalgia and arthritis. Some of these patients have acute attacks of pain suggesting renal colic, with irradiation towards the bladder but, although some proteinuria and pyuria occur, this disappears with the attack.

Investigation has failed to reveal any abnormality of the renal system. The disease is periodic but benign. Its diagnosis is difficult, as it has to be differentiated from a variety of conditions. No form of treatment to date has been of any avail.

(Continued on advertising page 45)

MEDICAL MEETINGS

THE TENTH INTERNATIONAL CONGRESS ON RHEUMATIC DISEASES—I

The incomparable setting provided by Rome's unique blend of the majestically ancient and the functionally modern was the site of the Tenth International Congress on Rheumatic Diseases. Such congresses are held every four years alternately in the eastern and western hemispheres under the auspices of La Ligue Internationale Contre le Rhumatisme. The program for the Tenth International Congress was capably and efficiently arranged by the host organization, the Italian Society of Rheumatology. The official opening ceremonies took place amid the impressive surroundings of the Campidoglio, Rome's city hall, on Sunday evening, September 3. Scientific sessions were held from Monday, September 4, through Thursday, September 7, in the Palazzo dei Congressi at the Esposizione Universale Roma (E.U.R.), a spacious, up-to-date real estate development originally designed as a world fair site in 1935. In all, some 1400 delegates and guests from all parts of the world registered at the Congress. The scientific program included no less than 460 papers, presented at the four plenary sessions, three symposia and multiple concurrent sessions. The latter appear to have become established as an integral component of such international gatherings, to the despair of the frustrated delegate who all too often finds himself confronted with the insoluble problem of being present in half a dozen rooms simultaneously if he wishes to hear all of the reports of interest to him.

In view of the massive scope of the scientific program, it is possible in a report such as this to touch upon but a few of its highlights.

RHEUMATOID ARTHRITIS

The results of a carefully conducted co-operative epidemiological study of rheumatoid arthritis in northern Europe were reported by LAINE (*Finland*), DE GRAAF (*Rotterdam*) and LAWRENCE (*Manchester*). Of a total sample of 4536 subjects, 3999 were examined, a completion rate of 88%. Among persons over 14 years of age in two northern England communities, 2.5% of males and 6% of females had "probable" or "definite" rheumatoid arthritis, based on the diagnostic criteria established by the American Rheumatism Association. In both sexes the prevalence increased with age, from 0.6% at age 15-24 in males to a maximum of 5% at age 55-64. Among females the prevalence rose from zero below the age of 35 to a peak of 16% in those 65 years of age and over. Radiological evidence of erosive arthritis in the hands and feet was observed in 3% of both males and females, but to a more severe degree in the latter. Erosive arthritis in the cervical spine was encountered in 5% of both sexes and this was the most frequent site of radiological changes, the prevalence of which reached maximums of 28% and 21% in males and females respectively, over the age of 75. It was noted, however, that over the age of 64, "senile" changes may simulate rheumatoid arthritis, radiologically, in the cervical spine, so that such findings must be interpreted with some reservation. The sheep cell agglutination test (SCAT) for rheumatoid factor was positive in 4% of males and 5% of females in the two northern England surveys, the prevalence of positive tests increasing stepwise with age to a maximum of 11% in males aged 65-74 and 9% in females aged 75 and over. The increase with age was not due to enhanced survival of seropositive individuals, nor did individuals as opposed to populations show an increasing titre with age. A possible explanation for these observations is that the SCAT titre depends on some antigen which has become less prevalent over the past 70 years, so that older citizens stand a greater chance of having acquired a positive test. It was suggested that periodic pandemics of infections such as tuberculosis, gonorrhea, syphilis and influenza, by exposing the population to repeated antigenic (bacterial) stimuli, may have influenced the prevalence of rheumatoid factor in the serum of subjects in the populations studied. Only one person in three with a positive SCAT in the random samples surveyed in these communities had clinical or radiological evidence of rheumatoid arthritis, so it is unlikely that this serum factor is often produced by the disease although there is evidence that a positive SCAT predisposes to rheumatoid arthritis. Within the areas of Finland, the Netherlands, England and Wales covered by these surveys, there was no evidence that geographic factors significantly influenced the prevalence of rheumatoid arthritis. On the other hand it appeared possible that local factors such as climate or occupation might influence the anatomic site of this disease. Rheumatoid serum factor was demonstrated in a greater proportion of persons in urban population as opposed to rural residents. A striking aggregation of rheumatoid arthritis within families was encountered in these studies. The relatives of persons with seropositive arthritis had four times the expected amount of clinical rheumatoid disease; the seronegative families twice the expected amount; and the relatives of healthy persons with a positive SCAT had exactly the expected amount of rheumatoid arthritis. It appears that in the families of both seropositive and seronegative rheumatoid arthritis, this disease is more prevalent than in the population as a whole, but only in the relatives of seropositive probands are more radiological erosive changes and positive serology found than would be expected. It was concluded, therefore, that at least two causative factors must be operating in these families, one responsible for symptoms and joint swelling, the other for positive serology and juxta-articular bone erosions. These causative factors may be environmentally or genetically determined; the relative importance of environmental and genetic factors remains to be determined and is the subject of further studies now in progress.

In their report of a long-term study of 200 patients with rheumatoid arthritis, followed up for approximately nine years after an initial period of hospital treatment by conservative measures, DUTHIE *et al.* (*Edinburgh*) commented that the need for accurate information about the course and prognosis of this disease remains as urgent as ever, particularly since new and more potent steroids are being developed and used in treatment without precise knowledge of the potential hazards of their long-term administration.

These authors considered it unlikely that the conservative measures employed in this study (bed rest, splinting, salicylates, physiotherapy and graduated return to optimum functional status attainable) altered the fundamental course of the disease. They confirmed the oft-stated dictum that 60% of rheumatoid patients can be maintained at a useful functional level for many years after their disease onset, by such simple therapeutic measures. It appeared reasonably certain that the prognosis is best for those patients whose disease has an acute onset and progressive course, and who are admitted to hospital for treatment within a year. The patient's age at onset had no marked prognostic influence and the ultimate outlook was essentially similar for both sexes. The response to treatment in hospital as measured by functional capacity and disease activity was a fairly reliable index of future progress. Isolated ESR readings provided no useful information as to prognosis, but serial records over a prolonged period did bear a relationship to the ultimate functional level. There was a highly significant relationship between the sheep cell agglutination test and progress of the disease, both in terms of disease activity and functional capacity. Consistently high SCAT titres carried grave prognostic significance. The presence of nodules, also, was usually associated with more severe disease. While it is impossible to forecast accurately the future of any rheumatoid patient being seen for the first time, the aforementioned features of the disease provide a valuable guide as to the likely future course and may assist in reaching a decision concerning the justification for use of more potent and hazardous forms of treatment.

VAN DAM and his co-workers at *Amsterdam*, in a study of 438 males and 776 females with rheumatoid arthritis, covering the period between 1946 and 1957, observed a death rate in both sexes that was 1.6 times as great as would be expected from the general mortality statistics for the Netherlands. The mortality for patients who attended for treatment after World War II was no more favourable than that of cases of longer duration, implying that duration of this illness does not influence the relation between the death rate due to rheumatoid disease and that of the general population. The mortality rate for patients with disease commencing before their 50th year was approximately double the general death rate; among those whose arthritis commenced after the age of 50, it was 1.5 times as great as the mortality rate for the population at large. "Rheumatoid arthritis" was the officially recorded, primary cause of death in 6.1% of this group of cases; "cardiac incompetence" and other non-specific heart disease in 21.6%; "cancer"—15.2%; cerebral vascular disease and its complications—9.5%; pneumonia—7.8%; glomerulonephritis—3.5%; pyelonephritis—0.4%; "other renal disease" 3.9%; coronary disease and myocardial infarction—4.3%; gastrointestinal ulceration and its complications—2.2%; tuberculosis—2.2%; valvular heart disease—2.2%; septicemia—1.7%; hypertension—0.9%; miscellaneous infections—0.9%; ulcerative colitis—0.4%; and accidents in 0.4%: in the remaining cases the primary cause of death was not specifically noted. The similarities and differences between the observations arising from this study and those of a similar investigation reported by COBB *et al.* in 1953 were noted.

MICHOTTE *et al.* (*Brussels*) referred to previous studies reporting evidence of a disturbed adrenaline-noradrenaline relationship in patients with chronic evolutive (rheumatoid) polyarthritis, and described their own investigations of the role of catecholamines in the pathogenesis of this disease. Normal controls and groups of rheumatoid patients receiving various forms of treatment, including prednisone, gold and iproniazid, were given intravenous infusions of C^{14}-labelled noradrenaline, following which their urine was examined for radioactivity, and the presence of urinary catabolites of noradrenaline was studied by chromatographic techniques. The results of these observations indicated that patients with rheumatoid arthritis showed an increased urinary excretion of radioactivity as compared with normal control subjects, after infusion of C^{14}-tagged noradrenaline. This exaggeration of noradrenaline catabolism in rheumatoid patients was further enhanced by certain of the pharmaceutical agents used in the treatment of rheumatoid arthritis coincident with induction of clinical remission as a result of such drugs as gold and corticosteroids. The acceleration of noradrenaline catabolism, which was linked to activation of mono-amino-oxidase, did not seem to play a role in the pathogenesis of rheumatoid arthritis but was interpreted rather as a defence phenomenon. Depression of this process by a mono-amino-oxidase inhibitor was not accompanied by clinical or biological evidence of improvement in the disease.

RHEUMATIC FEVER

SIOKAWA and WATANABE (*Tokyo*) described the results of light microscopic and electron microscopic studies of articular tissues obtained by punch biopsy from patients with rheumatic fever. Marked hypertrophy of the synovium and proliferation of synovial cells were observed in 13.3% of 45 knee joint biopsies; synovial atrophy in 44.4%; synovial surface roughening in 17.8%; adherent layers of fibrin on the synovial surface in 13.3%; synovial edema and hyperemia in 8.9%; capillary proliferation in 11.1%; endarteritis—17.8%; periarteritis and panangiitis, each in 2.2%; fibrinoid degeneration was noted in the synovium in 15.6%, in collagen of the capsule in 26.6% and in arterial walls in 6.7%; cellular infiltration was observed in the synovium in 26.7%, in connective tissue of the capsule in 6.7% and about the blood vessels in 11.1%. In all, abnormalities of the various types described were encountered in 40 of the 45 biopsies. Inflammatory cellular infiltrations were more prominent in the active stages of rheumatic fever. There was evidence that such manifestations of active rheumatic synovitis occurred most frequently in the early stages of the disease, particularly during the first attack, indicating that the activity of rheumatic fever tends to be less pronounced as the disease advances. It was reported that clinical signs such as joint pain, redness and swelling correlated statistically with the histological picture of inflammatory cell infiltration, synovial hypertrophy and proliferation, providing evidence that the clinical manifestations were due to the inflammatory lesions of articular tissue. Cellular infiltration was less prominent in those with congestive heart failure than in those without failure. These authors suggested that there may be two forms of rheumatic fever, according to the results of their studies, a "cardiac" type with mild articular lesions and an "articular" type with mild cardiac lesions. Laboratory tests indicative of disease activity, such as the ESR, serum mucoprotein levels, C-reactive protein and protein-bound polysaccharide or sialic acid levels, all correlated

significantly with the degree of inflammatory lesions in the biopsy specimens. Electron microscopic findings of an increase of irregularly outlined synovial cells with unevenly distributed microfibrils, were assumed to represent changes due to inflammation. As compared to a normal control specimen, the blood vessels in one rheumatic joint biopsy studied electron microscopically showed higher electrical density in the cytoplasm of their endothelial cells, narrower vascular lumina, thicker and more irregular basement membranes and unevenly distributed granules in the nuclei of pericytes.

ZALESSKY and DREISEN (*Moscow*) reported the isolation of more than 50 strains of a filtrable virus which they designated as "Virus R", from blood, heart, kidneys, spleen and the pharynx of "rheumatic" patients. All of these strains proved to be related in their antigenic and cultural properties. "Virus R" consistently caused, within two to four days after infection, rapid degeneration of human embryo fibroblasts in tissue culture and complete disintegration of the tissue. A cytopathogenic effect was noted in certain human and monkey tissue cultures differing from that produced by adenoviruses. "Virus R" also differed in its cultural and antigenic properties from viruses of the ECHO group, Coxsackie, poliomyelitis and others. Based on their observations that "Virus R" could be isolated only from "rheumatic" patients and that it was demonstrable by the immuno-histochemical method of Coons in inflammatory foci and in sections of the cardiac auricles obtained at biopsy, these authors proposed that this virus may constitute the etiological factor in some cases of rheumatic fever. In support of this thesis they reported the experimental production of typical "rheumatic endocarditis", with mitral stenosis, in a series of rabbits sacrificed and autopsied nine months after infection with "Virus R". Many aspects of this study were not clearly explained, particularly the clinical manifestations and the state of activity of the "rheumatic" disease in the patients from whom this mysterious new virus was recovered. It also appears to be a hazardous exercise indeed, to attempt to equate the changes described in these rabbits nine months after infection, with the rheumatic carditis of humans.

RUTSTEIN (*Boston*) and BYWATERS (*Taplow, England*) presented the results of a follow-up study completed five years after the termination of treatment of the 497 children admitted to the U.K.-U.S. co-operative clinical trial of the relative effectiveness of ACTH, cortisone and aspirin in the treatment of rheumatic fever. Of these, 445 (89.5%) were followed up for the complete five years and the cardiac status of 426 of them was known. The mortality in this group was strikingly low; only 16 (3.2%) had died, 14 of them from rheumatic heart disease. Thirty-six (7.2%) were untraced. At the end of the five years there was no evidence that the prognosis had been influenced more by one treatment than another, on the treatment schedules employed in this study. The major factor affecting the incidence of rheumatic heart disease after five years was the status of the heart when treatment was begun. Those without carditis initially had an excellent prognosis; 96% of these had no residual heart disease. In cases with carditis initially but no pre-existing heart disease the proportion without residual heart disease decreased progressively from 82% for those with only a grade I apical systolic murmur to 30% for those with failure and/or pericarditis initially. In patients with pre-existing heart disease the prognosis was poor. In this group only 30% without pericarditis or failure and none of those with pericarditis and/or failure were free of heart disease five years later. Patients with carditis initially and without pre-existing heart disease who developed rheumatic fever recurrences requiring re-treatment during the follow-up period had, on the average, a more severe cardiac status at the start of treatment than did those without such recurrences. After five years a larger proportion of the re-treated cases had murmurs. These results emphasized that the treatment of rheumatic fever cannot be properly evaluated unless the cardiac status of the patient at the start of treatment is taken into consideration.

LENOCH, KANKOVA and MARSIKOVA (*Prague*) observed that most patients with acute rheumatic fever can be treated adequately and satisfactorily by relatively large doses of aspirin or sodium salicylate. If larger doses are required, another form of salicylate such as calcium salicylate may be used in doses as high as 30 grams daily. Results comparable to those of sodium salicylate were said to have been obtained from treatment with 2,3 dihydroxybenzoic acid administered in divided doses every 2 hours for 16 hours each day, to a total dose which was one-third of the daily dose of sodium salicylate, i.e. to a daily total of 5 to 6 grams. The authors claimed that this compound has the greatest therapeutic activity of all the salicylates and is free from any significant side effects. The regimen described was said to have maintained blood salicylate levels higher than those considered by Coburn to be therapeutically effective, with peak levels as high as 13.5 mg. %. Hormonal therapy was advocated by these authors only for those patients with acute rheumatic fever who do not respond to the salicylate therapy as outlined, after a week of that form of treatment.

SYMPOSIUM ON GOUT

The much debated concepts concerning the nature of the metabolic disorders responsible for hyperuricemia and the clinical end-product, gout, were the subject of a number of far-ranging discussions in this symposium. SEEGMILLER and GRAYZEL (National Institutes of Health, *Bethesda, Maryland*) presented a convincing report in support of the concept that the hyperuricemia in this disease may indeed be related to more than one underlying metabolic derangement. These authors expressed the opinion that the two traditionally opposing views of pathogenesis, i.e. that which holds that hyperuricemia in gout is primarily due to uric acid overproduction and that which attributes this abnormality primarily to diminished uric acid excretion, may well be reconciled. This opinion was based on their evaluation of the magnitude of uric acid production and disposal in a group of 16 gouty subjects by means of three parameters: (1) the incorporation of glycine into urinary uric acid; (2) the turnover of isotopically labelled uric acid which also indicates the magnitude of extra-renal disposal of uric acid; and (3) the renal clearance of uric acid and of inulin. Five gouty subjects who showed no evidence of increased uric acid synthesis did show a significantly decreased urate/inulin clearance ratio. Among subjects who produced excessive amounts of uric acid, a group of individuals were identified, with urate/inulin clearance ratios in the same range as normal subjects in

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whom uric acid production was increased by administration of ribosenucleic acid (RNA). These observations led to the conclusion that the hyperuricemia of some gouty subjects is primarily of renal origin (impaired excretion) while that of others is primarily due to overproduction of uric acid. No evidence was adduced to indicate that diminished uricolysis was a consistent cause of hyperuricemia.

In contrast to the latter statement, BARCELO, SANS SOLA and MUSET (*Barcelona*) advanced a novel and interesting hypothesis involving the role of an oxidative enzyme, hepatocatalase, present in the liver, in the genesis of hyperuricemia and gout. These authors stated that hepatocatalase not only results in uricolysis in man, but may also affect purine biosynthesis through its oxidative action on formate, an important purine precursor. They postulated that a defect in this enzyme may be a significant factor, *per se*, or in association with other biochemical mechanisms, in the production of hyperuricemia and gout. They proposed that defective uricolysis may be added to the theories of excessive urate production and defective urate excretion by the kidney, to explain the pathogenesis of this disease. They reported clinical studies in which the intramuscular injection of hepatocatalase extracted from liver was followed by a prompt and striking decrease in blood uric acid levels, and in urinary urate excretion. In gouty patients, they stated that these biochemical effects were consistently associated with gradual clinical improvement manifested by reduction and sometimes cessation of acute gouty attacks as well as improvement in chronic gouty symptoms. Those with previous attacks of renal colic exhibited similar amelioration in this gouty manifestation. As well, tophi gradually decreased in size or disappeared after administration of hepatocatalase. No serious complications or side effects were encountered in association with treatment by this enzyme. Hepatocatalase has no anti-inflammatory action and is therefore of no value in the immediate treatment of acute gouty attacks. The authors also commented upon the pronounced hypocholesterolemic effect of hepatocatalase, which they feel warrants further investigation. The observations of these workers present an intriguing new avenue for investigation of the metabolic disturbance in persons with gout and hyperuricemia. If confirmed, these concepts could conceivably constitute a significant contribution to the understanding of pathogenetic mechanisms as well as to the treatment of gout.

WYNGAARDEN, JONES and ASHTON (*Durham, North Carolina*) described detailed biochemical studies providing evidence of an increase in turnover of phosphoribosylpyrophosphate (PRPP) in three gouty subjects who were hyperexcretors of uric acid. Since PRPP is an obligatory precursor of purine ribonucleotides, these data constitute additional evidence of overproduction of purines in this group of gouty subjects. Two gouty patients with normal uric acid excretion values showed normal values of PRPP turnover. Data obtained to date suggest, as do studies of glycine 1-C^{14} incorporation into urinary uric acid, that there may be a continuous gradation in magnitude of purine synthesis in man, and that some gouty subjects are normal by all methods currently available for evaluating rates of purine synthesis. Subjects with excessive rates of purine synthesis may have a faulty control mechanism for regulation of key early steps of purine production.

DELBARRE and RAKIC (*Paris*) reported on an inquiry conducted in 23 countries which indicated that gout, though exhibiting varying prevalence rates in different parts of the world, appears to be present universally in a geographic sense, and that the factor or factors responsible for it exist equally among white, black and yellow races. Factors that appear to incite this disease, however, are not equally potent in all countries. In considering its prevalence in different countries it must also be recognized that gout will only appear prominently in those nations where the average age of the population is relatively high, in view of the fact that the first attack occurs in the majority of cases after the age of 40. Since the average age of populations is increasing and since nutritional status is improving universally, it was predicted that gout is likely to increase in prevalence in all countries and that it will probably account for from 2% to 5% of all rheumatic disorders.

In discussion of the anti-inflammatory and uricosuric agents used in the treatment of gout, SERRE and SIMON (*Montpellier, France*) advocated the use of desoxymethylcolchicine by intramuscular injection, in preference to colchicine, in treatment of acute gouty attacks, because of its less drastic side effects. Corticosteroids should not be used for this purpose, according to these authors, because of the frequency of severe "rebound" attacks of gout after their administration is discontinued. Phenylbutazone is an additional effective anti-inflammatory agent that is of value in the treatment of acute gouty arthritis. Following the initial use of these anti-inflammatory agents, uricosuric drugs should be administered on a long-term basis. Sulfinpyrazone, probenecid and zoxazolamine are all effective uricosuric drugs. It was suggested that the value of combined treatment with two or more of these uricosuric agents may be worthy of investigation. Two types of "side effects" were encountered by these workers in patients receiving uricosuric therapy: (1) recurrent acute gouty attacks during the early weeks of their administration, and (2) attacks of renal colic which cleared satisfactorily when the dose of the uricosuric agent was reduced or its administration was discontinued. It was noted that in some cases hyperuricemia may persist after prolonged uricosuric therapy although these patients are much improved in all other respects.

KERSLEY (*Bath, England*), in a presentation of his observations and experiences with the use of various uricosuric agents in the treatment of gout, noted that sulfinpyrazone (Anturan) in doses of 400 mg. daily was a very effective uricosuric agent and on twice this dosage it was highly significantly more effective than probenecid (Benemid) or longacid (Urelim). It was, however, essential to continue this dosage regularly as intermittent administration three to four times a week allowed a marked rebound rise in plasma uric acid. No significant complications were associated with the use of sulfinpyrazone. Zoxazolamine (Flexin), 1.5 g. daily, was also a very effective uricosuric agent, comparing favourably with probenecid and having an effect roughly comparable to that of 400 mg. sulfinpyrazone per day, without serious toxic complications. In assessing combinations of uricosuric drugs it was found that 3.5 g. of aspirin completely eliminated the uricosuric effect of both sulfinpyrazone and zoxazolamine; 0.5 g. of aspirin had little if any effect in this respect, but as the dosage was increased its antagonistic

effect upon that of sulfinpyrazone progressively increased. On the other hand, the addition of longacid (Urelim) to sulfinpyrazone had a potentiating effect. The number of gouty attacks tended to increase during the first six weeks of treatment with both sulfinpyrazone and zoxazolamine, but thereafter attacks became less frequent and severe, and tophi tended to become softer and smaller. In the presence of persistent hyperuricemia, tophi and recurrent acute gouty attacks, Kersley at present recommends initiation of treatment with 400 mg. of sulfinpyrazone and 1.5 mg. colchicine daily, with a small dose of alkali and extra fluids. After three weeks the dose of sulfinpyrazone is increased to 600 or 800 mg. daily and after six weeks the colchicine is discontinued. Acute attacks are treated by 600 to 800 mg. of phenylbutazone daily for two days only.

OGRYZLO and co-workers (*Toronto*) emphasized that despite the questionable role of uric acid in the pathogenesis of acute gouty arthritis, the fundamental problem in chronic gout is the retention and accumulation of excessive amounts of uric acid in the tissues over a period of many years. Attempts at increasing its elimination through the kidneys remain the only practical method of dealing with this problem. Experience with the use of sulfinpyrazone over the five years since its introduction has confirmed initial claims that it is a highly effective uricosuric agent, and its virtual freedom from serious toxic effects makes it a suitable agent for prolonged maintenance therapy of chronic gout. It has no appreciable analgesic, antipyretic or anti-inflammatory properties. Its principal pharmacologic action appears to be a selective interference with the renal tubular transport system resulting in diminished reabsorption of uric acid filtered through the glomerulus, or alternatively increased secretion of uric acid by the tubules, although the latter has not been conclusively demonstrated in man in the presence of normal renal function. Detailed studies of sulfinpyrazone absorption and excretion and of 24-hour uric acid clearance during administration of this drug were described, as were the clinical and biochemical effects of long-term therapeutic trials in 69 gouty patients, extending over periods up to five years. In the dosages employed by these workers, the uricosuric effect of sulfinpyrazone was superior to that of probenecid, zoxazolamine, aspirin, phenylbutazone and thiophenylpyrazolidine. The uricosuric effect of sulfinpyrazone appeared to be sustained for prolonged periods and was associated with reduction in frequency of acute gouty attacks, normalization of serum uric acid levels, reduction in size or disappearance of tophi and improvement in debility. No serious toxic effects were encountered. The effectiveness of this drug is reduced in the presence of impaired renal function and it should be given only with great caution under such circumstances. Its uricosuric action is blocked effectively by aspirin, which should be avoided during treatment with sulfinpyrazone. The optimum dose appears to be 500 mg. daily given in two divided (night and morning) doses. In some cases doses as low as 200 mg. daily are adequate.

In summation of the foregoing discussions on the subject of gout, TALBOTT (*Chicago*), the chairman of this symposium, observed that this disease appears to be increasing in prevalence, possibly but not definitely in relation to developments of civilization. The concepts of pathogenesis now seem to have progressed through a cycle and returned once more to the belief that a certain proportion of cases at least are due primarily to impairment of renal excretion of uric acid, though another group of cases are presumably primarily due to excessive urate biosynthesis. The various possible biochemical findings in patients with this disease might be tabulated thus: (1) normal uric acid production as measured by today's techniques; (2) overproduction of uric acid; (3) hyperexcretion of uric acid; (4) normal excretion of uric acid; (5) impaired renal tubular excretion of uric acid; (6) normal renal tubular excretion of uric acid. There may well be other, as yet unrecognized biochemical abnormalities in addition to the foregoing, and in some patients, several of these six types of findings may coexist in varying combinations. Treatment has advanced and improved with the development of better uricosuric agents. These drugs do not appear to be indicated as soon as the first gouty attack occurs, but should probably be given after the second or third attack and continued on a long-term basis. The combination of "prophylactic" daily doses of colchicine together with a uricosuric agent was recommended. It may be possible in some cases, but not as a rule, to reduce the dose of uricosuric drugs after a few years of continuous administration. There is no definite evidence that the concurrent administration of alkalizing agents significantly reduces the incidence of renal stones in patients on long-term uricosuric therapy. The continued administration of a high daily fluid intake is more important in this respect. Uricosuric drugs can be continued despite the occurrence of occasional attacks of renal colic due to calculi. There is still no definite evidence that alcohol or dietary factors significantly affect the course of gout.

SYMPOSIUM ON IMMUNOLOGICAL ASPECTS OF RHEUMATIC DISEASES

Commenting on the overlap of autoimmune phenomena in certain thyroid diseases, lupus erythematosus and rheumatoid arthritis, HIJMANS (*Leyden*), DONIACH (*London*), ROITT (*London*) and HOLBOROW (*Taplow, England*) noted that it has been clearly established that autoantibodies to several normal thyroid constituents are present in the serum of patients with Hashimoto's disease and primary myxedema, and to a lesser extent in persons with thyrotoxicosis and other types of goitre, as well as in up to 10% of middle-aged women without overt thyroid disorders. Observations on thyroiditis patients have revealed an increased incidence in the patients, and their relatives, of other diseases in which hypersensitivity phenomena appear to be involved, such as rheumatoid arthritis, lupus erythematosus, progressive hepatitis and Sjögren's syndrome. A co-operative investigation was designed in the centres represented by these authors to determine whether patients with uncomplicated Hashimoto's disease have rheumatoid factor, antinuclear factors and other non-organ-specific antibodies, and also whether in lupus erythematosus and related disorders an increased incidence of thyroid antibodies might occur. Results of this study indicated that lupus patients without overt thyroid disorders have an increased incidence of low-titre antibodies to thyroglobulin. Many have high-titre complement fixation with crude thyroid extracts but this is non-organ-specific, and tests performed with thyrotoxic thyroid microsomes were mostly negative. Rheumatoid arthritis patients with negative L.E. cell tests showed no increase in thyroid antibodies.

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Uncomplicated Hashimoto cases with high-titre thyroid antibodies had negative L.E. cell tests and complement-fixation tests using nuclear materials as antigens. However, 5% to 10% were weakly positive by the fluorescent antinuclear factor test and a similar proportion gave autoimmune complement-fixation reactions with human organs. Rheumatoid factor was found only when clinical arthritis coexisted with thyroiditis. Patients with combined diseases gave positive results in both classes of antibodies corresponding with their clinical conditions. These observations suggested that although in Hashimoto patients autoimmune phenomena are as a rule strictly organ-specific and limited to the thyroid gland, there is some overlap with diseases in which immunological tolerance is more widely disturbed, and conversely that lupus patients are more prone to make antibodies to thyroglobulin.

ROTSTEIN and GOOD (*New York*) noted in a study of 41 patients with agammaglobulinemia that one-third suffered from such connective tissue diseases as rheumatoid arthritis, a "lupus-like syndrome", scleroderma and dermatomyositis. Thorough clinical, genetic, immunochemical, pathologic, histologic and bacteriologic investigations of this group of patients and studies of experimental models led these authors to the hypothesis that the connective tissue diseases in these cases result from infection, presumed to be of viral nature, though extensive attempts to demonstrate a virus have failed to date. It was postulated that if a virus were the etiological agent responsible for the connective tissue diseases in such patients, the following pathogenetic possibilities may exist: (1) the connective tissue disease may represent a direct response of the host to the infecting agent; (2) it may result from a hypersensitivity reaction to the infecting agent by a mechanism of delayed allergy; or (3) it may be a response to the infecting agent of another type of cellular hypersensitivity similar to but not identical with delayed allergy.

STEFFEN (*Vienna*) described the demonstration of connective tissue autoantibodies in rheumatoid arthritis serum by means of the antiglobulin consumption test, noting that the results of this test correlated with the clinical activity of the disease, and that it was positive in from 66 to 75% of the rheumatoid sera so studied. The properties of this connective tissue autoantibody were investigated by absorption-elution experiments, the eluates being studied by electrophoresis, ultracentrifugation and the antiglobulin consumption test. These studies indicate the existence in rheumatoid serum of a globulin fraction with connective tissue autoantibody properties which is similar to but distinct from the rheumatoid factors demonstrated by latex fixation and sheep cell agglutination tests.

HESS and ZIFF (*Dallas, Texas*), using the fluorescent antibody technique of Coons, reported the detection of presumably immune serum factors in a high proportion of patients with adult and juvenile rheumatoid arthritis; in others with rheumatic fever, other "connective tissue diseases", psoriatic arthropathy, ulcerative colitis, and in additional miscellaneous disorders including erythema nodosum, sarcoidosis, syphilis, cryoglobulinemia, "chronic pulmonary diseases", hepatic cirrhosis and undiagnosed hypergammaglobulinemia. This technique was also applied in an *in vivo* study of rheumatoid factor, specifically in an investigation of the interaction between rheumatoid factor and the cellular elements of the vascular system, and it was found to provide a sensitive test for the presence of the factor in the blood vessel walls. In their investigation of the possible presence of antibody to colon tissue in the serum of patients with ulcerative colitis, these workers demonstrated reactivity of the submucosal and occasionally of the muscle layers of normal human colon, with the sera of 11 of 34 patients with this disease, while 36 control sera gave negative reactions. Whether the serum factors thus demonstrated in rheumatic fever and ulcerative colitis are significant in the pathogenesis of these diseases is not known.

A considerable number of papers were devoted to reports of various studies of the rheumatoid factor. SVARTZ (*Stockholm*) described the methods employed for purification of this factor which is associated with a macroglobulin with a sedimentation coefficient of 18.8 Svedberg units, in which form it exists in the circulating blood. She noted that while rheumatoid factor has marked antigenic properties it does not behave as an antibody in the usual sense. She felt that the macroglobulin containing rheumatoid factor is formed as a result of special enzymatic processes, which, she suggested, were brought about by some infecting micro-organism. Attempts to induce in experimental animals a substance with properties similar to rheumatoid factor were most successful in white rats injected intraperitoneally with diplostreptococci of group B (*Streptococcus agalactiae* group), grown from the nasopharynx of patients with rheumatoid arthritis.

MORTEN HARBOE (*Oslo*) noted that anti-Gm factors in human sera are considered to belong to the rheumatoid factor(s), and that anti-Gm activity is rarely found in normals or persons with non-rheumatoid diseases. They are known to be 19 S gamma globulins whose solubility characteristics are similar to, if not identical with those of the factor(s) responsible for a positive Waaler-Rose test. This speaker described the results and techniques of an extensive battery of serological studies which, in conjunction with findings reported by other workers, led to the observation that the rheumatoid factor appears to consist of a heterogeneous group of closely related but nevertheless separate macroglobulins. Clarification of the nomenclature of these distinct substances was recommended as highly desirable to replace the present unprecise term, "rheumatoid factor".

Consistent with the comments of the aforenoted speaker were the results of column chromatography studies of proteins from rheumatoid patients' sera, reported by JONSEN, KASS and HVATUM (*Oslo*). These experiments showed that rheumatoid factor activity could be fractionated into three well-separated peaks. Two of these peaks were usually eluted with 0.125 M, pH 5.0 phosphate buffer. The agglutinating capacity of the individual fractions constituting each peak closely approximated the protein contents in the respective fractions. Chromatography of both cold-insoluble and acid-insoluble proteins gave identical results. Material from all three peaks precipitated with gamma globulin which had been heated for 10 minutes at 63° C. In addition to the peaks with rheumatoid factor activity, other protein fractions were eluted from the columns but the separation of these fractions seemed to be fairly distinct, as they produced no agglutination or precipitation with heated gamma globulin. Other studies of the proteins in the peaks with rheumatoid factor activity showed that this material contained proteins with different electrophoretic mobilities, indi-

cating the need for further purifications. These workers were careful to point out that the chromatographic separation of rheumatoid factor activity into several peaks could be due to artefacts and might not reflect the *in vivo* picture.

SHICHIKAWA, YAMAMOTO and FUJIOKA (*Osaka, Japan*), as a result of studies on the experimental production of rheumatoid factor, reported that an agglutinating factor closely resembling rheumatoid factor had been identified in the sera of rabbits immunized with *Salmonella pullorum*, group A hemolytic streptococci, *Treponema pallidum* or *E. coli*. These authors postulated that bacillary endotoxins are fundamentally linked with the experimental production of an agglutinating factor with properties similar to those of the substances in human rheumatoid serum that result in agglutination of sensitized sheep erythrocytes and F II coated latex particles.

KUNKEL and FUDENBERG (*New York*) noted that current evidence suggests that the rheumatoid factors represent antibodies to gamma globulin that may arise from mechanisms stimulated either by (a) the patient's own gamma globulin, native or altered; or (b) some foreign protein cross-reacting with gamma globulin. To investigate these two possibilities these authors studied the specificity of rheumatoid factors for the patient's own gamma globulin as well as for different genetic types of gamma globulin from other individuals. Isolated rheumatoid factors were mixed with different gamma globulin and the 22 S complex formation was observed in the ultracentrifuge. Ten different preparations of 19 S rheumatoid factors all complexed with each different type of gamma globulin tested. When added to normal sera, 22 S components formed and the sera resembled high-titre rheumatoid arthritis sera in the ultracentrifuge. All of the gamma globulin preparations complexed equally well and no genetic specificity could be demonstrated. Gamma globulin was then isolated from various sera of different types, aggregated and the aggregates were isolated. These all reacted with all rheumatoid factors tested and precipitin curves were obtained. Again, no specificity was obtained and aggregates of the patient's own gamma globulin reacted well with his rheumatoid factors. In contrast, in a system utilizing sensitized red cells coated with incomplete Rh antibodies, marked specificity could be demonstrated. Frequently the rheumatoid factors lacked specificity for the patient's own gamma globulin and reacted better with that of other individuals, suggesting the existence of iso-specificity that was not demonstrated with any of the other systems. These workers concluded that it seems probable that both auto- and iso-specificities exist, in a situation similar to that recently described for pancreatic antibodies in humans.

BUTLER and VAUGHAN (*Rochester, N.Y.*) presented their findings obtained in a study, by means of a direct serological method, of the reactivity of rheumatoid factor with gamma globulins from various sources. In keeping with findings already established in the sensitized human cell and the Gm systems, differences were observed in the reactivity of rheumatoid factor with the different individual human gamma globulins tested. Direct evidence was presented in support of the findings of others that rheumatoid factor is capable of reacting with autologous gamma globulin. It was established that rheumatoid factor has a broad spectrum of cross-reactivity with gamma globulin of other species.

WINBLAD (*Malmo, Sweden*) noted that rheumatoid factor can be demonstrated by a variety of techniques which include: (1) agglutination of hemolytic streptococci; (2) agglutination of homologous sensitized erythrocytes (sheep or human cells, anti-D-sensitized Rh positive human cells); (3) agglutination of particles suspended in or coated with gamma globulin (latex, acrylic, bentonite, collodion, mastic, tannic acid-treated erythrocytes); (4) precipitation of aggregated gamma globulin at 63° C.; (5) agglutination of tanned cells coated with aggregated (63° C.) gamma globulin and washed. Comparative studies of these various procedures led to the conclusion that the mechanisms involved in these reactions are probably fundamentally different. The serological reaction can be demonstrated without extra gamma globulin as a reactant, but the titre of rheumatoid factor so obtained is at a comparatively low level. The combination of non-aggregated gamma globulin and rheumatoid factor is more suitably demonstrated by plastic particle reactions, but the most satisfactory demonstration of such combination is obtained by precipitation reactions or by agglutination of tanned cells coated with aggregated gamma globulin.

SINGER, PLOTZ and EASON (*New York*) described a new modification of the latex fixation test for detection of antibodies or macroglobulins reactive with human gamma globulin. This technique uses previously coated 0.2 μ latex particles which, it was stated, are stable and permit reproducible results. The particles are coated with human gamma globulin, and the excess protein in solution is removed by repeated washing and high-speed centrifugation. These pre-coated particles were then used in latex fixation tests on 1150 sera. Of 200 rheumatoid sera, 74% gave positive results, compared with 1.3% of 150 controls. In 800 cases of non-rheumatoid diseases, results paralleled those of the standard latex fixation test, but the new procedure was more sensitive in the detection of macroglobulins. It was observed that a single batch of latex particles, pre-coated in this manner, remained stable for over a year if refrigerated at 4° C., and yielded completely reproducible titres.

A preliminary communication by DE BLECOURT, BOERMA and VORENKAMP (*Groningen, Netherlands*) concerned the role of heredity factors in rheumatoid arthritis patients with demonstrable rheumatoid factor in their sera, as compared with those whose Waaler-Rose and latex fixation tests remained negative. Immediate relatives (parents, brothers, sisters and children) of 31 seropositive and 31 seronegative probands with "classical" or "definite" rheumatoid arthritis (A.R.A. diagnostic criteria) were investigated. Of 226 relatives of seropositive probands, five had "definite" rheumatoid arthritis with both serological tests positive; five healthy relatives had positive latex tests; and three healthy relatives had positive Waaler-Rose tests. That is, 2.2% of relatives in this group had seropositive rheumatoid arthritis and 6% had rheumatoid factor demonstrable by one or both of the serological tests employed. In the 233 relatives of seronegative rheumatoid probands, one subject had seronegative, "definite" rheumatoid arthritis (0.45%); one healthy relative had positive Waaler-Rose and latex tests, and one healthy relative had a positive Waaler-Rose reaction only. In

the relatives of seronegative cases, therefore, one or both serological tests was positive in 0.9% of subjects. The difference between the incidence of positive serological reactions in the relatives of these two groups of probands is statistically significant ($p=0.05$). It was concluded that some hereditary factor may be involved in cases of seropositive rheumatoid arthritis, but evidence of such is lacking in the case of seronegative disease. The numbers involved in this study did not permit more definite conclusions, and more extensive, multicentre investigations of this problem were urged.

FALLET, MEYER and co-workers *(Geneva)* presented an analysis of studies of the FII latex fixation test on the sera of 1466 subjects since 1957. The object of this investigation was to determine the proportion of patients with rheumatoid arthritis, other rheumatic disorders, and non-rheumatic diseases who exhibited rheumatoid factor in their sera as demonstrated by this test. Certain of these cases were subjected to intensive clinical, radiological and immuno-electrophoretic investigations. As a result of these studies it was concluded that although the FII latex test is not specifically diagnostic for rheumatoid arthritis it is a valuable diagnostic aid (84% positive). Unfortunately it is all too often negative in the earlier stages of the disease when it would be of particular value. This observation is not without exception, however, as was demonstrated by the finding of a strongly positive latex test in one patient two weeks after the apparent clinical onset of her disease. In this case it was suspected that rheumatoid factor was likely present before the rheumatoid arthritis became clinically manifest. These authors reported decreased latex fixation titres or conversion of positive tests to negative in some rheumatoid patients receiving gold therapy, paralleling the degree of clinical improvement in such cases. They were unable to elucidate any significant differences between latex-positive and latex-negative cases of "chronic evolutive polyarthritis" except for a greater incidence of radiological changes in the sacroiliac joints in the latter cases. They interpreted the consistently negative tests in patients with ankylosing spondylitis as evidence in support of the concept that this disease is not the same entity as rheumatoid arthritis. They also noted a relatively high incidence of positive latex fixation tests in patients with liver disease, particularly cirrhosis (47.1%), disseminated lupus erythematosus (36.4%), Waldenström's macroglobulinemia (16%), "certain infectious processes" (12.1%), and diabetes mellitus (9.8%). They were unable to define the factor responsible for this reaction by electrophoretic analyses or by immuno-electrophoresis.

In their report of a clinical and serological study of 50 patients with juvenile rheumatoid arthritis, TOUMBIS, MCEWEN, FRANKLIN and KUTTNER *(New York)* noted that rheumatoid factor was demonstrable in the sera of 87% of these patients by the very sensitive sheep erythrocyte inhibition technique although the usual serological tests for this factor were positive in a much smaller proportion and when positive, the titres were lower than those encountered in adults with rheumatoid disease. A survey of blood relatives of these children revealed rheumatoid factors in the serum of 17% of the relatives studied. Four of the latter had clinical evidence of rheumatoid arthritis, and the remainder were asymptomatic. This is four times the percentage of positive results in non-rheumatic control subjects and is essentially similar to the findings in blood relatives of adults with rheumatoid arthritis. These workers are of the opinion that the clinical and serological similarities in adult and childhood cases indicate that "Still's disease" is the same fundamental disorder as rheumatoid arthritis in adults.

Clinical, pathological and serological studies of 40 patients with Sjögren's syndrome were described by BLOCH, BUNIM *et al. (Bethesda, Md.)*. Rheumatoid factor was detected in significant titre in every case, including those without clinical evidence of rheumatoid arthritis. All of the Sjögren cases with myopathy, and most of those with the "sicca syndrome" alone, had hyperglobulinemia. Antinuclear factor was found in 77% of the series, but L.E. cells were detected in only three of the 40 patients and all these had "classical" rheumatoid arthritis. Complement fixing antibodies against diverse human and animal tissue components were present in 83% of those with the "sicca syndrome" alone or with accompanying myopathy. Eleven of the 40 patients had circulating antibodies against thyroglobulin and two of these had Hashimoto's thyroiditis. Myopathy, confirmed electromyographically and histologically, was a prominent clinical manifestation in four cases in this series, proximal muscle groups being affected in all instances. Arteritis was found in random skin and muscle biopsies in three patients with Sjögren's syndrome who did not have rheumatoid arthritis and who had never received corticosteroid therapy. Three other patients with accompanying rheumatoid arthritis also showed arteritis on muscle biopsy but such biopsies failed to demonstrate arteritis in 17 other cases in the series. The high frequency of rheumatoid factors and other abnormal circulating factors or antibodies to tissue components is of unusual interest. The enhanced immunological reactivity and multiple system involvement observed in Sjögren's syndrome suggest an analogy to systemic lupus erythematosus (SLE). The characteristic histological changes in the salivary and lacrymal glands in Sjögren's syndrome are strikingly similar to those in the thyroid in Hashimoto's thyroiditis. Since both Hashimoto's thyroiditis and SLE are considered by many to be autoimmune diseases, the same hypothesis may apply to Sjögren's syndrome though substantiation of this is, as yet, lacking.

GOSLINGS and co-workers (*Leyden*) presented a report on investigations designed to ascertain whether rheumatoid arthritis with accompanying L.E. cells should be considered as a variant of rheumatoid disease or as a form of SLE; and secondly, whether the presence of L.E. cells correlated with a different clinical picture or influenced the prognosis in rheumatoid arthritis. Groups of rheumatoid patients with and without L.E. cells were thoroughly studied initially and again five years later. The following conclusions were presented. The L.E. cell phenomenon is highly specific for the so-called "collagen diseases". The symptomatology of rheumatoid arthritis (R.A.) with L.E. cells was different from that of R.A. without L.E. cells. The former showed a higher frequency of splenomegaly, lower respiratory tract disease, abnormal urinary sediment, anemia, false positive serological tests for syphilis, elevation of ESR, failure of the latter to decrease after gold therapy, and a higher incidence and titres of positivity of the Waaler-Rose test. After

a five-year period these differences were less pronounced and no more statistically significant. After an average duration of disease of 14 years there was no convincing evidence that R.A. with L.E. cells should be regarded as a form of SLE. To the time of reporting, the presence of L.E. factor did not appear to have influenced the mortality rate. The authors stressed that these observations are applicable only to the cases they studied, and before they can be accepted with finality they must be confirmed by more extensive studies over a longer period of time.

VORLAENDER (*Bonn, Germany*) described the following results of clinico-immunologic studies of patients with rheumatic carditis: Statistical analysis of 107 cases indicated that the activity of rheumatic inflammation is reflected immunologically in ESR elevation, increase in C-reactive protein, alpha-2 and gamma globulin, and persistent elevation of antistreptolysin titre; all of these manifestations, in conjunction with the clinical picture, are therefore of diagnostic and prognostic value, though none is specific for rheumatic inflammation. Beyond these expressions of disturbed immunologic phenomena, chronic progressive forms of rheumatic carditis and those with rheumatic reactivation after commissurotomy, exhibit the presence of an additional immunological factor directed against an antigen located in the endomyocardium. This antigen appears to be of a complex nature, consisting of a bacterial (streptococcal) fraction and a portion related to the cardiac tissue, probably a glucopolypeptide. By serial immunoelectrophoretic examination of endomyocardial tissue containing rheumatic lesions it was demonstrated that transferrin, gamma globulin and glucoproteids were present in that tissue in significantly increased amounts. Comparative experimental studies on rabbits confirmed that, as in clinical rheumatic carditis, an isoantibody effect on the myocardium favours a simultaneous streptococcal infection of cardiac tissue. These observations may help to explain the clinically well-recognized susceptibility to bacterial superinfection in rheumatic endomyocarditis and underline the importance of the prophylactic use of penicillin.

DONALD C. GRAHAM

(To be concluded in the next issue of *The Journal*)

PUBLIC HEALTH

SURVEILLANCE REPORT OF EPIDEMIC OR UNUSUAL COMMUNICABLE DISEASES

Canada

PARALYTIC POLIOMYELITIS

Twenty-seven cases of paralytic poliomyelitis have been reported to the Epidemiology Division during the four-week period from August 6 to September 2, 1961.

Reporting continues at a comparatively low level. The provinces of Quebec, Alberta and Ontario, with 43, 24 and 15 cases respectively, account for 85% of the cases reported in Canada to date.

Only three deaths have occurred so far this year—two from Alberta and one from Quebec. For the corresponding period in 1960, 55 deaths had been reported.

The four-week totals (week 32 to week 35) and the cumulative totals to week 35 for the past five years are presented below:

Year	*1961*	*1960*	*1959*	*1958*	*1957*
Four-week period week 32 to week 35.....	27	238	552	53	31
Cumulative total to week 35.....	97	629	955	99	92

To date, preliminary individual case reports have been received on 50 cases from two provinces, Quebec and Ontario. This constitutes 51.5% of the total cases.

MUMPS

About 100 cases of mumps have been reported in the Cape Broyle and Fermuse area of Newfoundland for the week ending August 26.

INFLUENZAL MENINGITIS

A case of influenzal meningitis has been reported in a three-month-old Eskimo boy from Fort Churchill, Manitoba. He was admitted to the Fort Churchill Military Hospital on August 14 with head retraction, fever and bulging fontanelle. Examination of the cerebrospinal fluid confirmed the diagnosis of influenzal meningitis.

ASEPTIC MENINGITIS

Three cases of aseptic meningitis were reported at Bonnyville, Alberta, some 180 miles northeast of Edmonton. The presenting symptoms were frontal headache, neck stiffness, vertebral pain and fever. The first case occurred on July 22, 1961. Last year in this area, similar cases of aseptic meningitis were followed three weeks later by the occurrence of cases of poliomyelitis.

STREPTOCCOCAL SORE THROAT

Twenty cases of streptoccocal sore throat have been reported from West Hants, Nova Scotia, for the week ending August 26; the first case appeared on August 5.

TYPHOID FEVER

A confirmed case of typhoid fever has been reported from Holman Island in the Northwest Territories, and an additional suspected case has been evacuated to the Charles Camsell Hospital in Edmonton. The outbreak has been attributed to bad fish.

TRICHINOSIS

Eleven more cases of trichinosis have been reported from the Province of Quebec. Five of these cases occurred in Jonquière, two in Arvida, and one each in Kenogami, Montreal, Richmond and Victoriaville. This brings the total to 64 cases for the year.

TETANUS

One case of tetanus has been reported from Nova Scotia for the week ending July 29 (delayed report).

AMEBIC DYSENTERY

A case of amebic dysentery has been reported in a 32-year-old Indian from the Island Lake Reserve at Loon Lake, Saskatchewan. He was transferred to the University Hospital at Saskatoon on August 18 because of liver involvement and imminent bowel perforation. Emergency ileostomy was performed on August 23 and diagnosis was confirmed by the laboratory isolation of *Iodamoeba bütschlii*.

The patient's father died in the University Hospital on July 20, 1959, with perforation of the large bowel caused by amebic dysentery. The family, other members of the reserve and other contacts are under close observation. It is unlikely that further cases will occur.

Attempts to isolate the plague bacilli from wild animals in the area involved have so far been unsuccessful.

CHOLERA

Hong Kong

Over 160 cases and 17 deaths have occurred from cholera in this Crown colony. All transportation companies are requiring travellers from Hong Kong and area to possess valid vaccination certificates. Strict surveillance is being exercised at Canadian ports on arrivals from Hong Kong to ensure that the disease will not gain entry into Canada.

Epidemiology Division, Department
of National Health and Welfare.
Ottawa, September 15, 1961.

PARALYTIC POLIOMYELITIS IN CANADA*
36TH WEEK—ENDING SEPTEMBER 9, 1961

	Reported cases									*Deaths*		
	This week			*Last week*			*To this date*			*To this date*		
	1961	*1960*	*1959*	*1961*	*1960*	*1959*	*1961*	*1960*	*1959*	*1961*	*1960*	*1959*
Canada	4	52	141	6	71	162	104	681	1096	3	58	97
Newfoundland	1	11	10	1	3	15	8	39	92	—	4	6
Prince Edward Island	(a)	—	—	—	—	1	—	—	2	—	—	—
Nova Scotia	(a)	—	—	—	—	1	1	9	3	—	1	—
New Brunswick	—	5	7	—	1	2	1	70	25	—	1	3
Quebec	—	24	82	4†	29	101	46†	202	770	1	25	68
Ontario	—	2	23	1	3	23	15	21	96	—	1	9
Manitoba	—	—	2	—	—	7	—	8	21	—	1	1
Saskatchewan	1	3	4	—	3	2	4	46	24	—	6	1
Alberta	1	13	8	—	22	4	25	135	28	2	8	2
British Columbia	1	4	5	—	10	6	4	151	24	—	11	3
Yukon	—	—	—	—	—	—	—	—	—	—	—	—
Northwest Territories	—	—	—	—	—	—	—	—	11	—	—	4

*Weekly returns based on telegraphic reports by provinces.
(a)Figures not available.
†Delayed report.

GASTRO-ENTERITIS

Following a wedding reception in St. Nicholas, Lévis County, Quebec, on August 26, 60 to 70% of the guests came down with acute gastro-enteritis.

PLAGUE

United States

To date, three cases of plague have originated from the Santa Fe-Pecos area of New Mexico. The first case was diagnosed in the latter part of June in a 38-year-old sawmill worker. He was admitted to hospital on June 24 and died four days later. At no time did he produce the bloody sputum characteristic of pneumonic plague.

The second case appeared in a 38-year-old geologist who had been working in an area approximately ten miles west of Santa Fe. He was admitted to hospital in Boston, Mass., on July 20 and died on July 29. Autopsy revealed a shallow ulcerative lesion of the hand, regional adenopathy and evidence of intravascular hemolysis. Blood cultures were found to contain both beta hemolytic streptococci and plague bacilli.

The third case occurred in a 23-year-old lineman for a power and light company who was working in the Pecos area, the site of exposure of the first reported case. He was admitted to hospital on August 4 with enlarged inguinal nodes suggestive of plague; the diagnosis was confirmed by an agglutination titre of 1:80 on the patient's convalescent serum. The patient made a rapid and complete recovery.

PAGES OUT OF THE PAST: FROM THE JOURNAL OF FIFTY YEARS AGO

We all know how unsatisfactory it is to empty a uterus of a hydatid mole with a curette or placental forceps, even when aided with the fingers in the uterus. The procedure, in addition, is not devoid of risk from excessive hæmorrhage or from perforating the uterus. Dorman reports a case of death from hæmorrhage and shock. Similar cases are found in the literature. H. Freund relates three instances in which he had to do an abdominal Cæsarean section, owing to profuse hæmorrhage.

I was led by chance to a procedure which I deem of great value. One of my cases was a primipara, pregnant about five months, suffering from eclampsia and comatose, with a tightly closed cervix. I was desirous of emptying the uterus as quickly as possible. I decided, therefore, to do a vaginal Cæsarean section, although I was not aware I had to deal with a hydatid mole. I was enabled thereby, to pass my entire hand into the uterus and shell out all the vesicles with such ease and precision, and with so slight a loss of blood, that I was greatly impressed with the advantage of the method in all cases of this abnormality. The patient made a rapid and satisfactory convalescence.—Hiram N. Vineberg, *Canad. M. A. J.*, 1: 958, 1911.

BOOK REVIEWS

SURGERY IS DESTINED TO THE PRACTICE OF MEDICINE. Hunterian Oration, Royal College of Surgeons of England. Sir Reginald Watson-Jones. 79 pp. Illust. E. & S. Livingstone Ltd., Edinburgh; The Macmillan Company of Canada Limited, Toronto, 1961. $3.60.

The Hunterian Oration was founded in 1813 by John Hunter's nephew, Dr. Matthew Baillie, and his brother-in-law, Sir Everard Home. It is presented before the Fellows and Members of The Royal College of Surgeons of England and their invited guests. It celebrates the anniversary of Hunter's birth, and the orator receives the title of Hunterian Professor of the Royal College of Surgeons. Most of the orations are published later in book form.

In his address Sir Reginald Watson-Jones directed attention to the mementos of John Hunter which had survived the bombing of the College buildings during World War II. One of the great treasures of the College is the portrait of John Hunter by Sir Joshua Reynolds. This picture had an interesting history. It was originally painted in 1786, but Reynolds was dissatisfied with the result and four years later Hunter returned for further sittings. In Ottley's "Life of Hunter", published in the early 1830s, it is recorded that Hunter was a fidgety sitter and that Reynolds in a fit of desperation had turned the canvas upside down and had painted a completely new portrait over the old one. Sharp's well-known engraving of Hunter was made from the original portrait and shows a much younger and more forceful person. Watson-Jones became interested in the story, which had remained unchallenged for over a century. He felt the existing portrait did not do justice to Hunter, and at his request x-ray studies were made by Mr. Ian Rawlins, the scientific adviser of the National Portrait Gallery. These films showed that the canvas had not been reversed and that the chief changes had been in the head and face of the portrait. This is an interesting example of the results to be obtained by modern methods of research in the realm of art.

The orator then went on to describe the professional life of John Hunter, the unpleasant experiences of Hunterian orators during the Lancet-Wakley/Royal College disagreements of the 1820s and 30s, and the unending battles over priority of publication in the field of medicine. John Hunter and his brother were no strangers in these battles. Watson-Jones himself drew attention to Hey Groves, an earlier Hunterian Professor, having introduced the pin operation for fractures of the femur some 15 years before the Smith Petersen nail.

Then came a discussion of the material suggested by the title of the oration—The Decline of Cutting Operations in Surgical Treatment. Using the Case Books of Agnes Hunt for illustration and making frequent references to the work of Sir Robert Jones, he described the early days of orthopedic surgery and the progress made since those days by advances in surgical skill and the invaluable help of the antibiotics in pyogenic infections: "No longer is there need for the sequestrectomies and scraping of sinuses, the operations that were so often repeated year after year, six, eight or ten operations in one patient." Early recognition and the use of appropriate medical orthopedic measures would avoid the necessity of later surgery in many of the deforming diseases.

The oration ended with a panegyric on the outstanding contributions made to the College by the most eminent of its Past-Presidents, the late Lord Webb-Johnson, and the orator pointed out how these new activities might be continued and extended into even broader fields of endeavour.

The book is eminently readable, and beautifully printed. It contains a great deal of material which will be of value not only to the specialist in orthopedics but also to those who have an interest in the history of medicine.

EXPLORATIONS INTO THE NATURE OF THE LIVING CELL. Robert Chambers and Edward L. Chambers. 352 pp. Illust. Harvard University Press, Cambridge, Mass.; S. J. Reginald Saunders and Company Limited, Toronto, 1961. $8.80.

For almost a century medical students have studied microscopic anatomy and learned to identify tissues by their cellular morphology. This study utilizes killed and stained tissue, and seldom if ever are living cells examined. Yet it is the living cell that produces the changes that are the basis for cellular pathology.

Robert Chambers recognized this and for more than 40 years studied living cells. He not only observed but also manipulated developing techniques and equipment for microdissection and the injection of single living cells. For these studies, unicellular animals and eggs of marine forms were commonly used. He was able to make major contributions to the knowledge of the intimate cellular details of fertilization.

This volume is the summary and critical assessment of his life work. The importance of this work is becoming more evident as more studies are centred upon cellular metabolism. The techniques developed by Chambers provide a method of manipulating and making injections into single living cells.

It will be a convenient reference book for all who are working on single isolated cells.

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CLINICAL MEDICINE AND THE PSYCHOTIC PATIENT. O. F. Ehrentheil and W. E. Marchand. 383 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $11.75.

This book is obligatory reading for those who work with psychotic patients and can be read with advantage by many doctors. The authors treat the physical ailments of the mentally ill in a large psychiatric hospital of the U.S. Veterans' Administration. Their book consists of a series of papers which they and their colleagues have written over the years. This method has its disadvantages. There is always some redundancy in such collections of papers and also rather disconcerting omissions in such collections which would have been eliminated had a text been written in the usual way. The redundancy is not noticeable here. But there are some omissions, and one hopes that the authors, who are widely experienced and knowledgeable, will distil their experience into a brief and inclusive text on the same subject before long. Until that time this book must have a place in every mental hospital library and in libraries of psychiatric units in general hospitals.

The authors have three main themes: firstly, the variety of special problems which the advent of physical illness produces in patients who are already psychotic. History taking, examinations, and treatment can all be complicated, particularly if the physician is unaware of the sort of thing he must be on the alert for. Secondly, the illnesses seen in mental hospitals have few counterparts outside. There is an interesting section on megacolon, another on the complications of deep insulin treatment, and an excellent discussion of the exhaustion syndrome which is becoming less frequent than it used to be, but from the author's figures it is still a very grave and usually fatal illness. Feeding difficulties and the complications of electroshock therapy are not discussed and this is a serious gap in an otherwise excellent book. In third place are those illnesses which are thought to be less frequent in mental hospitals. The authors consider that, while the supposed low incidence of diabetes and neoplasms is probably due to faulty case finding, psychotic patients generally and schizophrenics in particular enjoy an unexpected immunity from allergies and rheumatoid arthritis. Although they do not actually say so, it seems from their figures and case histories that schizophrenics are also peculiarly resistant to wound and surgical shock.

While these findings are undoubtedly of medical interest, they also raise questions about the possible humoral pathologies in the so-called functional psychoses. There is much else besides in this meaty book which is certainly the best which the reviewer has seen in its field.

A SYNOPSIS OF PHYSIOLOGY (RENDLE SHORT). 5th ed. Edited by C. C. N. Vass. 348 pp. Illust. John Wright & Sons Ltd., Bristol; The Macmillan Company of Canada Limited, Toronto, 1961. $5.00.

This well-condensed little book contains much valuable information. After having learned physiology from the usual textbooks, students will benefit from using it to check and revise their knowledge before an examination.

Thirteen years have elapsed since the last edition of this Synopsis. Considering the vast advance made in some sections of physiology, the time was ripe for a new edition. If any criticism can be raised against this edition, it is that it attempts to cover too large a field, including for instance large sections which today form part of biochemistry. It also includes some historical data which perhaps could be dispensed with in a work of this type. On the other hand, some modern concepts or current hypotheses of physiology have been omitted. No mention is made of the countercurrent principle, of the mode of transport of thyroid hormones in the blood, of ionized Ca in connection with the parathyroids, of the mode of action of insulin, of the limbic system or of conditioned reflexes.

Considering the difficulties in condensing a large discipline, Dr. Vass has achieved a good result in this work.

BLEEDING SYNDROMES. A Clinical Manual. Oscar D. Ratnoff. 287 pp. Illust. Charles C. Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1960. $9.25.

This recent book is well written and easily read. It is not intended as a laboratory manual, or as a reference to all the available literature, although the bibliography is quite extensive, but as a guide to the understanding and care of patients with bleeding disorders.

There are 223 pages of text and 45 pages of bibliography. Although there are some charts and tables, there are no illustrations, so that the book is all text and somewhat less expensive than it would be otherwise.

The chapter on afibrinogenemia and fibrinolysis is detailed and excellent, as is the section on hemophilia and related diseases, but the reviewer would have preferred a more detailed description of the vascular forms of purpura and their relationship to other bleeding disorders. On the other hand, thrombocytopenia is considered at great length.

This book is well recommended for the physician who wishes to become up-to-date on bleeding problems, and for the postgraduate medical student boning up for his specialty examinations in internal medicine.

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DIE ERKRANKUNGEN DER GALLENWEGE UND DES PANKREAS. Diagnostik, Klinik, und Chirurgische Therapie (The Diseases of the Biliary Tract and Pancreas--Diagnosis, Clinical Features, Surgical Therapy). Walter Hess. 672 pp. Illust. Georg Thieme Verlag, Stuttgart, W. Germany; Intercontinental Medical Book Corporation, New York, 1961. $35.50.

This excellent monograph on the disorders of the biliary tract and the pancreas is divided into nine sections, the first of which deals with anatomy and physiology. In this portion the illustrations showing the variants of the hepatic, cystic and pancreatic ducts and the hepatic and cystic arteries deserve special mention. The next two sections contain an exhaustive account of the pathology, clinical findings and diagnostic procedures, as well as several chapters on differential diagnosis. A special section is devoted to radiomanometry (operative cholangiography with pressure measurements), and the great importance of this procedure in the recognition of stenosing papillitis and tumours, strictures and stones in the choledochus and hepatic ducts is clearly shown. It is apparent that the so-called post-cholecystectomy syndrome would be less frequent if radiomanometry were carried out in all operations on the biliary tract.

Section 5 contains detailed systematic descriptions of the operative procedures related to the biliary tract and the pancreas, each of which is accompanied by clear illustrations. In the next chapters the indications for these operations, and their sequelae and limitations, are discussed. This is followed by a guide of how to proceed in any situation that may be encountered by the surgeon. The last three sections deal with preoperative measures and anesthesia, postoperative course and complications, and late postoperative complaints.

The book is well organized and written in a fluent style which makes for pleasant reading. The work is based on extensive clinical experience and a thorough knowledge of the world literature. The author expresses his opinion clearly without being dogmatic. The illustrations and radiographs are excellent, and the typography is flawless. The book is highly recommended to surgeons and internists who can read German.

SOMATIC TREATMENTS IN PSYCHIATRY. Pharmacotherapy; Convulsive, Insulin, Surgical, and Other Methods. Lothar B. Kalinowsky and Paul H. Hoch in collaboration with Brenda Grant. 413 pp. Grune & Stratton, New York; The Ryerson Press, Toronto, 1961. $9.75.

In this volume the authors produced a book which will undoubtedly become as much of a bible to psychiatrists in training and many others as their original "Shock Treatments in Psychiatry".

The section on pharmacotherapy is the most notable new feature. The older and more widely used agents such as chlorpromazine are presented with a brief history of their development, physiological and pharmacological properties, clinical effects, dosage, psychiatric indications, side effects and complications. The less widely used and newer agents are reviewed briefly, covering chemistry and pharmacological properties, mode of administration and dosage, complications and current views of their therapeutic effectiveness. Phenothiazines and Rauwolfia alkaloids are discussed under the heading of neuroleptics, the term tranquillizers being reserved for the mild non-barbiturate sedatives such as the meprobamates. This chapter also deals with the "psychoanaleptics" (imipramine), the monoamine oxidase inhibitors and the stimulants. Finally there is a short section on the therapeutic use of psychotomimetics and a brief account of the use of combinations of drugs.

Under the chapter heading "The Convulsive Therapies" the authors give a particularly clear evaluation of the current status of this therapeutic approach. The history of convulsive therapies is touched on, with comments on camphor and metrazol, the major part of the chapter being devoted to electric convulsive therapy, as well as the less widely used electric narcosis, and electrostimulatory non-convulsive therapy. Consistent with the wide interest and concern regarding premedication for electroconvulsive therapy, particularly the muscle relaxants, the advantages and disadvantages of their use are cogently discussed.

In another chapter the authors deal with insulin coma treatment. They stress their belief that this treatment should not be dropped from psychiatric therapies, although they agree that at our present stage of knowledge, like other physical therapies, the basis for its use remains empirical, and its value can be established only on clinical usage rather than theoretical expectations.

Psychosurgery is reviewed perhaps most circumspectly of all, in keeping with the drastic reduction in its application since the appearance of the neuroleptic drugs. The views regarding its indications are clearly described. A variety of miscellaneous treatments such as carbon dioxide therapy, continuous sleep, and hormone therapy are reviewed. The final chapter on theory discusses some of the current views on the pathophysiological mechanisms underlying the major mental disorders and the light that has been thrown on them through the development and investigation of the somatic treatments used in psychiatry.

This text has no more than the usual number of typographical errors that seem to plague scientific books when compared with other types of publications, but it has its share. The table of generic and brand names in the first chapter is badly printed and consequently quite confusing. These are minor defects and far outweighed by good features such as the extensive bibliography.

MEDICAL NEWS *in Brief*

(Continued from page 900)

THE USE OF INCINERATORS IN URBAN AREAS

Part I.—Domestic Units

There are two broad approaches to the disposal of garbage, rubbish and domestic wastes in urban areas. These are based on approved practices that conform to air pollution control and related regulations. In the first case, the garbage, after collection, is disposed of in land-fill operations. This method is employed extensively in municipalities where vacant or waste land is readily available. The second approved practice is to burn the garbage in properly designed large-scale municipal incinerators.

The use of small domestic incinerators for the combustion of garbage and domestic wastes is, in general, not considered acceptable in many urban areas because of difficulties concerned with air pollution and odour nuisances. Although incinerators are employed in large buildings, such as apartments, commercial and public buildings, hospitals and industrial plants, in certain cities, the design and operation of these incinerators require approval by the local air pollution control department. The recent trend in connection with the use of incinerators is to discourage their application in such cases and to incinerate the garbage in large-scale municipal incinerators. The problems relating to small domestic incinerators are discussed by Katz (*Occup. Health Bull.*, Vol. 16, No. 9, 1961).

The basic incinerator design standards for the combustion of waste that is common to dwellings and apartments contain the following specifications:

1. The incinerator should contain primary and secondary combustion chambers and should be equipped with an auxiliary burner.
2. The incinerator should have sufficient thickness of refractory lining or insulation to prevent excessive and destructive heating to adjacent materials and construction.
3. The incinerator should be so designed that it can be operated to conform to air pollution control regulations. These usually require that the emission of fly ash should not exceed 0.85 lb. per 1000 lb. of flue gas, corrected to 12% carbon dioxide content, and that no smoke in excess of No. 2 Ringlemann should be discharged for more than four minutes in any 30-minute period.

Various tests of domestic type incinerators have been made from time to time. In an investigation carried out at the University of Detroit in 1956 on 14 representative gas-fired domestic incinerators the results indicated that none of the units was satisfactory. It was reported in the conclusions of this investigation that:

"Even if the incinerator is designed and constructed for complete odourless combustion, the operator would be the housewife, who, in most cases, would not be skilled in the firing technique required and she certainly would not invest the time and trouble necessary to follow firing methods required for complete combustion."

The experience of the Commissioner of the New York Department of Air Pollution Control, Dr. Leonard Greenburg, is that refuse

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A NEW ERA IN ANTICOAGULANT THERAPY ...LONG-TERM MAINTENANCE

"Not only will patients live longer on long-term anticoagulant therapy, but they will on the whole lead a fuller and more comfortable existence."[1]

Extensive experience over the past ten years has demonstrated the value and practicality of *long-term* anticoagulant therapy in selected cases of myocardial infarction and related disorders, to prevent thromboembolic episodes and extend life expectancy.[1-6]

Friedberg,[2] in his survey covering 3,254 cases, has pointed out that *mortality is reduced* at least one-third to one-half and that when anticoagulant therapy is properly administered under controlled conditions, *major hemorrhage is rare.*

A decade of experience with "Danilone" (phenylindanedione) has shown that this anticoagulant is effective, safe, and economical in long-term use, providing one of the cornerstones of successful anticoagulant therapy.

For a free copy of the new 16-page *Report on the Increasing Practicality of Long-Term Anticoagulant Treatment*, write to the Medical Department, Charles E. Frosst & Co., P.O. Box 247, Montreal 3, Quebec.

ORIGINAL "Frosst" CONTRIBUTION TO WORLD-WIDE ANTICOAGULANT THERAPY

"DANILONE"

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Supplied: **50 mg.** (white—scored) **25 mg.** (yellow—scored)

"... more easily controlled, much less expensive ... the long-term anticoagulant of choice."

Oliver, M.F.: Brit. M.J. **1**:1176, 1959

DOSAGE: INITIAL DOSAGE varies over a wide range. The most frequently recommended initial dose is 200 mg. divided into two doses 12 hours apart. Some authors have found that, in about 50% of cases, 500 to 600 mg. may be required in the first 24 hours.[7] Such large doses should be used with caution and avoided in patients with congestive heart failure and in those over 65 years of age. MAINTENANCE DOSAGE also varies over a wide range—between 25 and 250 mg. daily being required. *Bottles of 100.*

CAUTION: If hemorrhage occurs, the drug should be withdrawn immediately and, when necessary, 25 to 50 mg. of vitamin K_1 should be administered. Sensitivity reactions (skin rash, pruritus, diarrhea, agranulocytosis, fever, jaundice) have occurred but they are very rare. In cases where the urine is alkaline, it may become orange-red in colour due to the excretion of alkaline salts of "Danilone" or its metabolites. This colour reaction should not be mistaken for hematuria.

Also available: "DICUMAROL" (brand of bishydroxycoumarin U.S.P.) in 50 mg. and 100 mg. tablets, bottles of 100.

1. Connell, W.F.: Canad. M.A.J. **76**:664, 1957. 2. Friedberg, C.K.: New York J. Med. **58**:877, 1958. 3. Stephens, C.A.L., Jr.: Arizona Med. **17**:499, 1960. 4. Report of the Working Party on Anticoagulant Therapy in Coronary Thrombosis to the Medical Research Council: Brit. M.J. **1**:803, 1959. 5. Manchester, F.: Ann. Int. Med. **47**:1202, 1957. 6. Nichol, E.S. *et al.*: Am. Heart J. **55**:142, 1958. 7. Beamish, R.E. and Carter, S.A.: Canad. M.A.J. **74**:39, 1956.

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may be disposed of most economically by collection from the source and reduction in efficient central incinerators, rather than in small units of the domestic type.

A recent study by the Philadelphia Air Pollution Control Section has indicated that domestic incinerators of the gas-fired type cannot properly be called smokeless and odourless.

The Los Angeles County Air Pollution Control District has banned all single-chamber domestic incinerators whether gas-fired or not.

The Province of Ontario Air Pollution Control Act of 1958 (as amended in 1959) contains a clause which empowers the council of any municipality to pass by-laws for prohibiting or regulating the emission from any source of air contaminants or any type or class thereof. The following section from this clause relates to the prohibition on the production of an air pollution nuisance from the operation of domestic incinerators:

"for prohibiting,

"any person to operate, or to cause or permit to be operated, an incinerator for the disposal of scrap, waste material, rubbish, garbage, or any combination thereof in such a way as to cause air pollution".

It is clear, therefore, that the operation of domestic incinerators in such a manner as to prevent the creation of an air pollution or odour problem involves careful design of equipment and care in the combustion of household garbage or wastes.

Apartment and domestic incinerators, in addition to having variable nature and rate of feed, also have disadvantages in that no collector system has been devised that is over 75% efficient and reasonable in cost, and the operators are invariably amateurs. In general, very numerous complaints are received in cities in which apartment and domestic incinerators are used.

In New York and many other cities, apartments destroy much of their refuse by flue-fed incinerators. When these are fitted with air pollution control equipment, they are expensive and require more maintenance. The use of flue-fed incinerators in the future is now a matter of doubt, as apartment owners do not wish to pay the extra cost of the modern equipment, and it may be that apartment refuse will soon all be collected for incineration in a municipal plant.

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ROLE OF SALICYLATES IN MASSIVE GASTROINTESTINAL HEMORRHAGE

Investigations have shown that stress of different types, including physical and emotional trauma, and infection, is the primary cause for gastric erosions, and may be the sole cause for the incidence of hemorrhage of the gastrointestinal tract. However, it has also been shown, clinically and experimentally, that salicylates can cause occult gastrointestinal bleeding. Although the exact mechanism is unknown, the appearance of bleeding from various organs (nose, genitourinary tract, and uterus) independent of the gastrointestinal tract suggests that this is due to systemic effects of salicylates, and not to local effects.

Kossover and Kaplan (*Am. J. Gastroenterol.*, 35: 445, 1961) sug-

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gest that the effect is probably on the basis of increased capillary fragility and the non-specific effects of stress. Thus, in the presence of stress, salicylates may be responsible for a reasonable percentage of massive gastrointestinal hemorrhages, cause undetermined, as well as hemorrhage from activation of known gastrointestinal pathology.

From July 1, 1959, to January 1, 1960, these investigators report that there were 45 cases of massive gastrointestinal hemorrhage at Touro Infirmary, New Orleans, Louisiana. Forty-six per cent of these patients had taken salicylates within a 24-hour period prior to admission to hospital. Radiographs taken during or after the hemorrhage revealed active peptic ulcer to be present in 37% of cases, while normal gastrointestinal series were recorded in 19%. The final diagnosis was peptic ulcer in 69% of the cases; hemorrhagic gastritis, cause undetermined, in 8%; hemorrhagic gastritis due to aspirin, 8%; hemorrhage, cause undetermined, 15%.

It is concluded that: (1) prolonged salicylate analgesics should not be used in the presence of ulcer, active or inactive; (2) the surgeon should always keep in mind the possibility that salicylates could be the cause of massive upper gastrointestinal bleeding; and (3) after a subtotal gastrectomy in cases in which no definite bleeding site is found in chronic aspirin users, further salicylates should be withheld postoperatively.

EVALUATION OF A NEW CHOLECYSTOGRAPHIC AGENT

Oragrafin, the sodium salt of β - (3 - dimethylamino - methylenamino - 2,4,6 - tri - iodophenyl)-propionic acid, is a new cholecystographic medium for oral administration. The recommended dose is 3 g.

Cholecystographic studies, using oragrafin, were carried out by Brannan, Donovan and Hodgson (*Proc. Staff Meet. Mayo Clin.*, 36: 197, 1961) on 300 patients, 130 males and 170 females, ranging in age from 12 to 80 years. Analysis of the cholecystograms indicated that oragrafin is a reliable contrast medium. The incidence of side effects was very low. In this series there were no serious reactions, and only 11 transient reactions were reported.

The rapidity with which oragrafin is excreted in amounts sufficient to provide visualization of the gallbladder is a most desirable characteristic. In most cases a period of three hours was sufficient to allow the making of a cholecystogram. The agent is apparently excreted from the liver, often in visible amounts, and it is further concentrated in the gallbladder. Although it is often excreted in concentrations sufficient to permit visualization of the biliary ducts, such a degree of visualization was not present often enough in this series, however, to be considered a uniform characteristic of the drug when used in routine cholecystography. Strict attention to the time interval and the use of specialized roentgenographic technique would undoubtedly result in a higher percentage of visualization of the biliary ducts.

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Butazolidin prices have been reduced fifteen per cent. In the ten years which have elapsed since Butazolidin was first placed in clinical trial, almost 2000 published reports from clinics throughout the world have substantiated it as the leading non-hormonal agent in the therapy of arthritic disorders.

When you prescribe Butazolidin® your choice is verified by a decade of world-wide experience.

MEDICAL NEWS *in brief*

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MORTALITY STATISTICS IN U.S.A.

Despite the marked progress made in life conservation, more than one-third of the deaths in the United States are among people under age 65, according to the statisticians of the Metropolitan Life Insurance Company.

About 575,000 people a year die before reaching age 65, not counting the toll in the first year of life. Premature death is considerably more frequent among males than among females, the mortality rate at ages 1-64 years being 4.8 and 2.7 per 1000, respectively, for the two sexes in 1958.

Accidents are the predominant cause of death among children and young adults, accounting for three-fifths of the total mortality among males at ages 15-24 and for nearly one-third of the total among females at these ages. Cancer, mainly leukemia, ranks second as a killer at ages 1-24.

As early as ages 25-44, the cardiovascular-renal diseases outrank all the other causes of death among males. Among women at these ages, however, cancer is the leading cause of death and takes nearly twice as many lives as heart disease.

There are more than 400,000 deaths a year in the 45 to 64 year age group, about three-fourths of them being due to the cardiovascular-renal diseases or cancer.

POSTGRADUATE COURSE IN DERMATOLOGY, UNIVERSITY OF BUFFALO

The University of Buffalo School of Medicine will offer a postgraduate course in dermatology on November 8 and 9, 1961. The major skin diseases seen in clinical practice are included in this course. Registrants will have an opportunity to examine a considerable number of patients with skin diseases and discuss their differential diagnosis and treatment with the faculty. The tuition fee is $30.00. Applications should be addressed to: Mary A. Lorenz, R.R.L., Department of Postgraduate Education, University of Buffalo School of Medicine, 3435 Main St., Buffalo 41, N.Y., U.S.A.

VIIth INTERNATIONAL CONGRESS FOR INTERNAL MEDICINE

The VIIth International Congress for Internal Medicine will take place under the Chairmanship of Professor Dr. Wollheim, Würzburg, from September 5 to 8, 1962, in Munich (Federal Republic of West Germany).

The main topics will be:

(1) Immune processes in the pathogenesis of internal diseases (diseases of the blood, kidney, thyroid, heart and vessels).

(2) Shock and collapse in internal medicine (pathogenesis, hemodynamics, clinical forms and consequences of shock and their therapy).

(3) Environment and disease (rheumatic disease, hypertension, diabetes, arteriosclerosis, coronary artery disease).

For information, write The Secretariat of the VIIth International Congress for Internal Medicine, Schwalbacher-Strasse 62, Wiesbaden, Deutsche Bundesrepublik. (Telegraphic address: INTERMED, Wiesbaden.)

TELEVISION IN MEDICAL EDUCATION

A two-year study of the use of television for medical-dental education and research will be made by the Council on Medical Television of the Institute for Advancement of Medical Communication (*A.M.A. News*, August 21, 1961).

The five main divisions of the study will be:

An illustrated reference inventory of abstracts of articles on applications of TV to medical-dental education and research.

A comprehensive survey of TV as it is currently being used in 27 medical and 17 dental schools. Diagrams and photographs will supplement this section.

A TV systems analysis guide to provide educators and administrators with a framework in which advance planning and decisions concerning the extent and type of TV facilities needed can be made.

An illustrated compendium of tested and practical architectural, structural and mechanical modifications of commercially available TV components that improved TV instrumentation as teaching devices.

A catalogue of videotape presentations designed for postgraduate medical-dental education. Emphasis will be on presentations prepared specifically for open-circuit TV transmission.

When completed, copies of the study will be available to all institutions, organizations and schools concerned with the health-science professions.

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TREATMENT OF SUPERFICIAL PHLEBITIS AND THROMBOPHLEBITIS BY A PENETRATING ANTISEPTIC CREAM

Forty-six patients with superficial phlebitis and thrombophlebitis were treated topically with a cream containing 1% silver dinaphthylmethane disulphonate (a modified formulation of "viacutan cream" which contains added lissapol). All 46 patients in this series, reported by Alant (*Practitioner*, 186: 753, 1961), had failed to respond to conventional conservative methods of treatment, or had been sent into hospital by their own doctor. All patients were confined to bed, and the foot of the bed was raised 20 cm. Between 2 and 5 ml. of the cream (depending upon the size of the area) was applied daily with gentle firm massage to the skin over the inflamed vein. Mobilization was achieved gradually, and when the patients were ambulatory an elastic bandage was applied.

The average healing time in this series was 10 days, which is slightly, but significantly, less than the time taken to heal 60 comparable unselected cases by conventional methods.

The treatment with this cream was found to be simple, safe, and effective. There seem to be no contraindications and no danger of untoward side effects. However, this treatment is only short-term, as it cannot affect the underlying predisposition to phlebitis and thrombophlebitis. The underlying etiology and the factors predisposing to the condition must be considered separately and treated in conjunction.

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MEDICAL NEWS *in brief*

(Continued from page 55)

CANCER INSTITUTE AND SOCIETY APPOINTMENT

Dr. E. E. Tieman, O.B.E., for 25 years a medical officer and administrator in the Canadian armed forces, has been appointed assistant executive director of both the National Cancer Institute of Canada and the Canadian Cancer Society. In this capacity he will assist Dr. R. M. Taylor.

A native of Dashwood, Ont., Dr. Tieman obtained his M.D. degree from the University of Western Ontario in 1935. He has been in uniform continuously since 1936 when, after an internship at Hamilton General Hospital and a brief medical practice in Tavistock, Ont., he joined the permanent active militia. During World War II he went overseas with the 5th Canadian Armoured Division, later serving with the 3rd Canadian Infantry Division in Northwestern Europe and commanding both base and field medical units.

In December 1942, for distinguished service, he was awarded the Order of the British Empire. Towards the end of the war he became divisional surgeon of the 6th Canadian Infantry Division with the rank of colonel and later was commanding officer of the 2nd Canadian Hospital Ship *Letitia* in the Pacific Theatre.

Since the war Dr. Tieman has been commanding officer of the London, Ont., Military Hospital, area medical officer for Western Ontario and command medical officer of the Army's Eastern Command, Halifax—the last from 1951 to 1955. Recent positions have been: director of the Medical Joint Training Centre in Toronto and, since last October, commandant of the Canadian Forces Medical Service Training Centre at Camp Borden. In 1956, he obtained the Diploma in Public Health from the University of Toronto.

ABDOMINAL EXPLORATION FOR GASTROINTESTINAL BLEEDING OF OBSCURE ORIGIN

The records of 100 consecutive patients with gastrointestinal bleeding of obscure origin who had undergone abdominal exploration for diagnostic purposes at the Mayo Clinic were reviewed by Retzlaff, Hagedorn and Bartholomew (*J. A. M. A.*, 177: 104, 1961). The patients had had melena or hypochromic anemia, but not hematemesis. In every case thorough, and often repeated, medical evaluations had failed to reveal the cause of the bleeding.

Results of surgical exploration were positive in 30% of the patients, and indeterminate in another 17%. In the remaining 53% of the patients, no lesion was found that could account for the bleeding. The most common findings in the positive cases were peptic ulcer, malignant disease and diffuse disease of the small bowel, in that order.

Follow-up information obtained on 48 patients who had had negative results at exploration revealed that in 21 of these bleeding had stopped spontaneously though no specific treatment had been given, and in 27 there had been further bleeding postoperatively. In only four of these 48 patients was a definite diagnosis ever es-

tablished: re-exploration in three of the four patients revealed leakage from an aortic graft into the duodenum in one, carcinoma of the transverse colon in another, and peptic ulcer in the third; in the fourth patient a primary bleeding defect, plasma thromboplastin component (PTC) deficiency, was demonstrated.

Analysis of the cases indicated that the best candidates for exploratory operation in cases of gastrointestinal bleeding of obscure origin were: (1) patients in the middle and older age groups, (2) patients who had severe bleeding requiring many transfusions, and (3) those having only occult bleeding.

Abdominal exploration should be seriously considered in most patients with gastrointestinal bleeding in whom the diagnosis cannot be established by the usual methods, since 10% of the patients in this series proved to have malignant disease.

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PRIMARY MYOCARDIAL DISEASE

Fowler, Gueron and Rowlands have recorded the case reports of 18 patients from a large U.S. university hospital who died of congestive heart failure without clinical or pathological evidence of a primary cause (*Circulation*, 23: 498, 1961). Their ages at death were from 18 months to 68 years. There were 14 males and four females; 11 were white and seven were Negro. Seven patients had had heart failure for five years or more; and three had had heart failure for over 10 years. Seven patients were alcoholics and three had nutritional cirrhosis.

Transient mitral or tricuspid systolic murmurs and apical protodiastolic gallop rhythms were common. Atrial fibrillation was present in six patients. The electrocardiograms revealed an abnormal degree of left-axis deviation in three and left bundle-branch block in two. Right-heart catheterization was performed in four of these patients and showed low cardiac output, increased arteriovenous oxygen difference, and elevation of pulmonary arterial, pulmonary wedge, right ventricular diastolic, and right atrial pressures. These findings are not specific and occur in congestive heart failure.

Heart weight was over 500 g. in 13 patients; all 18 had left ventricular hypertrophy. Mural thrombi were present in 10; six had pulmonary emboli and three had systemic arterial emboli. One patient had gross myocardial scarring; only two had small accumulations of inflammatory cells in the myocardium. Ten had focal increase of elastic tissue.

Primary myocardial disease may simulate coronary heart disease because of the abnormal electrocardiogram; it may simulate hypertensive heart disease because of elevation of diastolic blood pressure during heart failure in some patients; it may simulate pericardial effusion because of the poor cardiac pulsations, narrow pulse pressure, and paradoxical pulse. It may simulate rheumatic heart disease because of the apical systolic and diastolic murmurs, left atrial enlargement, and presence of Kerley lines. The cause of this disease is unknown.

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MEDICAL NEWS *in brief*

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ACUTE GLAUCOMA AFTER GENERAL SURGERY

At the University Hospital, New York Medical Center, approximately 5000 major surgical procedures are performed each year. A review of all of these cases during a recent five-year period revealed five instances of acute glaucoma arising within 72 hours after surgery. The case histories of these patients, 3 female and 2 male, ranging in age from 52 to 72 years, have been described by Wang, Tannenbaum and Robertazzi (*J. A. M. A.*, 177: 108, 1961).

Possible etiological factors are considered, and include (1) a preexisting narrow ocular filtration angle, (2) mydriasis induced by stress through endogenous catecholamine, (3) elevation of intraocular tension from succinylcholine, and (4) pupillary dilatation caused by scopolamine.

An adequate history regarding previous eye disease and a preoperative evaluation of anterior chamber depth are advisable in all patients. Shallow chambers, prior glaucoma, and/or the symptoms of blurred vision, haloes around lights, and ocular pain should be considered as relative contraindications to elective surgery until ophthalmologic examination is performed.

In such "risk patients" preoperative miotic drops, such as 2% pilocarpine, should be used in the eyes before anesthesia is begun, and scopolamine and succinylcholine should be avoided if possible.

In the early postoperative period, the eyes of every patient should be examined for signs of acute congestive glaucoma (cloudy corneas, pericorneal vascular congestion, or dilated fixed pupils). Any symptoms of acute glaucoma (ocular pain, blurred vision) should be quickly evaluated and appropriate treatment instituted.

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SMOKING AND HEALTH

A study involving 43,068 persons over the age of 30 showed a variety of physical complaints associated with cigarette smoking habits. Hammond, of the American Cancer Society (*Arch. Environ. Health*, 3: 146, 1961), said that associated complaints included coughing, hoarseness, shortness of breath, chest pains, loss of appetite, nausea and vomiting, stomach and abdomen pains, diarrhea, loss of weight, easy fatigue and insomnia. He said that some of the complaints showed "a high degree of association with smoking", notably coughing, shortness of breath and loss of appetite.

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AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next scheduled examination of the American Board of Obstetrics and Gynecology (Part I, written, will be held in various cities of the United States, Canada, and military centres outside the Continental United States, on Friday, January 5, 1962.

Current Bulletins may be obtained by writing to: Robert L. Faulkner, M.D., Executive Secretary and Treasurer, 2105 Adelbert Road, Cleveland 6, Ohio.

Diplomates of this Board are urged to notify the Office of the Executive Secretary and Treasurer of any change in their address.